Circulation Research Compendium on Hypertension

The Epidemiology of Blood Pressure and Its Worldwide Management
Genetic and Molecular Aspects of Hypertension
Hypertension: Renin–Angiotensin–Aldosterone System Alterations
The Sympathetic Nervous System Alterations in Human Hypertension
Obesity-Induced Hypertension: Interaction of Neurohumoral and Renal Mechanisms
The Structural Factor of Hypertension: Large and Small Artery Alterations
Inflammation, Immunity, and Hypertensive End-Organ Damage
Clinical Value of Ambulatory Blood Pressure: Evidence and Limits
Sodium Intake and Cardiovascular Health
Randomized Controlled Trials of Blood Pressure Lowering in Hypertension: A Critical Reappraisal
New Approaches in the Treatment of Hypertension

Giuseppe Mancia, Guest Editor

New Approaches in the Treatment of Hypertension

Suzanne Oparil, Roland E. Schmieder

Abstract: **Hypertension is the most common modifiable risk factor for cardiovascular disease and death, and lowering blood pressure with antihypertensive drugs reduces target organ damage and prevents cardiovascular disease outcomes. Despite a plethora of available treatment options, a substantial portion of the hypertensive population has uncontrolled blood pressure. The unmet need of controlling blood pressure in this population may be addressed, in part, by developing new drugs and devices/procedures to treat hypertension and its comorbidities. In this Compendium Review, we discuss new drugs and interventional treatments that are undergoing preclinical or clinical testing for hypertension treatment. New drug classes, eg, inhibitors of vasopeptidases, aldosterone synthase and soluble epoxide hydrolase, agonists of natriuretic peptide A and vasoactive intestinal peptide receptor 2, and a novel mineralocorticoid receptor antagonist are in phase II/III of development, while inhibitors of aminopeptidase A, dopamine β-hydroxylase, and the intestinal Na^+/H^+ exchanger 3, agonists of components of the angiotensin-converting enzyme 2/angiotensin(1–7)/Mas receptor axis and vaccines directed toward angiotensin II and its type 1 receptor are in phase I or preclinical development. The two main interventional approaches, transcatheter renal denervation and baroreflex activation therapy, are used in clinical practice for severe treatment resistant hypertension in some countries. Renal denervation is also being evaluated for treatment of various comorbidities, eg, chronic heart failure, cardiac arrhythmias and chronic renal failure. Novel interventional approaches in early development include carotid body ablation and arteriovenous fistula placement. Importantly, none of these novel drug or device treatments has been shown to prevent cardiovascular disease outcomes or death in hypertensive patients. (*Circ Res*. 2015;116:1074-1095. DOI: 10.1161/CIRCRESAHA.116.303603.)**

Key Words: blood pressure ■ drug ■ hypertension ■ interventional ■ treatment

Hypertension is the most common modifiable risk factor for cardiovascular disease (CVD) and death; the increased risk associated with blood pressure (BP) elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage. A total of 69 drugs in 15 different classes, many of which are also available in single pill combinations, have been approved for the treatment of hypertension in the United States.[1] Despite this plethora of treatment options, an

Original received October 9, 2014; revision received December 4, 2014; accepted December 11,2014. In January 2015, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 14.7 days.

From the Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama (S.O.); and Department of Nephrology and Hypertension, University Hospital of the University Erlangen-Nürnberg, Germany (R.E.S.).

Correspondence to Suzanne Oparil, MD, Vascular Biology and Hypertension Program, 1720 2nd Ave South, ZRB 1034, Birmingham, AL 35294. E-mail soparil@uab.edu

Nonstandard Abbreviations and Acronyms

ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting-enzyme inhibitor
Ang I	angiotensin 1
Ang II	angiotensin 2
Ang III	angiotensin 3
Ang IV	angiotensin 4
ANP	atrial natriuretic peptide
APA	aminopeptidase A
APN	aminopeptidase N
ARB	angiotensin receptor blocker
AVF	arteriovenous fistula
BAT	baroreflex activation therapy
BNP	B-type natriuretic peptide
BP	blood pressure
CB	carotid body
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
EDLF	endogenous digitalis-like factors
HF	heart failure
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
RAS	renin angiotensin system
RDN	renal denervation
s-EH	soluble epoxide hydrolase
SHR	spontaneously hypertensive rat
TRH	treatment resistant hypertension

estimated 10% to 15% of the general hypertensive population has resistant hypertension, defined as uncontrolled BP on ≥3 antihypertensive drugs of different classes, including a nonpotassium-sparing diuretic, at optimal doses, or requiring ≥4 drugs to achieve control.[2,3] In addition, ≈0.5% of hypertensive patients have refractory hypertension, defined as uncontrolled BP on ≥5 drugs.[4]

Many more hypertensive patients are uncontrolled because of nonadherence or intolerance to available antihypertensive agents. Recent drug monitoring studies have revealed nonadherence to BP lowering therapy in 25% to 65% of patients with apparent treatment resistant hypertension (TRH).[5–9] In 24% to 34.5% of these individuals, who were prescribed 3–5$^+$ antihypertensive medications, no antihypertensive medication was detected in blood or urine samples. The unmet need of controlling BP in these high-risk patients may be addressed, in part, by the development of new drugs and devices and procedures that are designed to treat hypertension and comorbidities, such as heart failure (HF), chronic kidney disease, and diabetes mellitus. This review will summarize recent development of novel drugs classes and interventional strategies for the treatment of hypertension and related target organ damage.

Part I. New Drugs

Anti-Aldosterone Agents

Aldosterone is a mineralocorticoid that regulates electrolyte and volume homeostasis in normal subjects and, when elevated, can contribute to the development of hypertension and a variety of related pathologies, including myocardial hypertrophy and fibrosis and HF.[10] The principal effector of aldosterone action is the mineralocorticoid receptor (MR), a nuclear transcription factor that is expressed at high levels in the cortical collecting duct of the kidney (Figure 1). Activated MRs stimulate expression of sodium channels, resulting in increased sodium and water reabsorption and potassium loss, leading eventually to a volume expanded form of hypertension. Activation of MRs in extra adrenal tissues, particularly the heart and blood vessels, also promotes the development of hypertension and CVD by upregulating NADPH oxidase and increasing production of reactive oxygen species. This reduces the bioavailability of nitric oxide and leads to endothelial dysfunction and vascular disease.

Aldosterone is synthesized from 11-deoxycorticosterone in the zona glomerulosa of the adrenal cortex via the action of a mitochondrial cytochrome P450 enzyme, aldosterone synthase, which is encoded by the CYP11B2 gene[11] (Figure 1). Aldosterone synthase catalyzes the final 3 rate-limiting steps of aldosterone synthesis (11β-hydroxylation of 11-deoxycorticosterone to form corticosterone, followed by 18-hydroxylation of corticosterone to form 18OH-corticosterone, and 18-oxidation of 18-OH corticosterone to form aldosterone). Cortisol synthesis, which occurs in the zona fasciculata of the adrenal cortex, is mediated by 11β-hydroxylase, which is encoded by the CYP11B1 gene.[11,12] CYP11B2 has a high sequence homology with CYP11B1, and both CYP11B2 and CYP11B1 share an 11β-hydroxylase reaction, creating problems for those attempting to design selective aldosterone synthase inhibitors.[12–14]

Mineralocorticoid Receptor Antagonists

MRs have been therapeutic targets in hypertension treatment for over half a century: the first MR antagonist (MRA), spironolactone, appeared in the early 1960s.[15] Although spironolactone monotherapy has modest BP lowering efficacy, it has had a recent resurgence as add-on therapy in patients with resistant hypertension[16–19] and in the treatment of HF.[20] Spironolactone use has been limited by its lack of selectivity for the MR, particularly at higher (>25 mg) doses. Because of its structural similarity to progesterone, spironolactone has significant progestogenic and antiandrogenic activity, leading to troublesome adverse effects in both men and women.[21,22] The more selective MRA eplerenone lacks the antiandrogenic effects of spironolactone, but is less potent and has a shorter (3–4 h) half-life, leading to reduced antihypertensive efficacy and a requirement for twice daily dosing.[22,23]

The search for newer nonsteroidal MRAs that have superior selectivity and affinity for the MR began with the observation that some dihydropyridine calcium channel blockers compete with aldosterone for binding to the ligand binding domain of the MR and decrease aldosterone-mediated recruitment of transcriptional coactivators that are necessary for MR-directed DNA transcription.[22,24,25] Optimization of MRA activity of dihydropyridine compounds led to the development of BAY 94-8862 (finerenone), a nonsteroidal MRA that has greater selectivity than spironolactone for the MR over other steroid hormone receptors, greater affinity than eplerenone for the

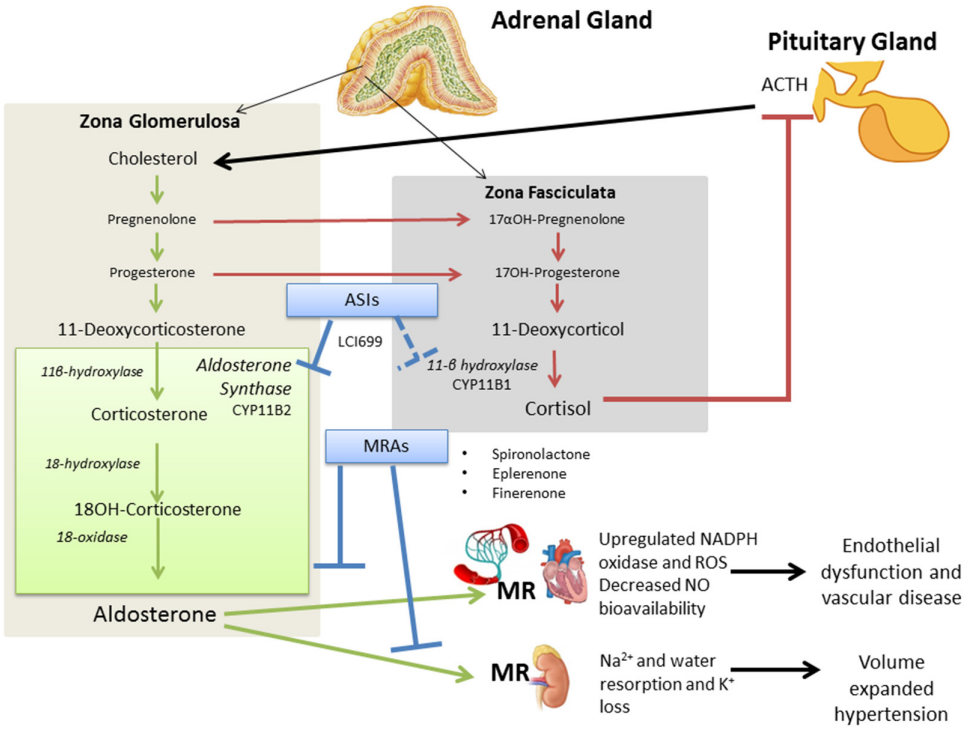


Figure 1. Mechanism of action of anti-aldosterone agents. Aldosterone synthase inhibitors (ASIs), such as LCI699, inhibit the rate limiting step of aldosterone production. Mineralocorticoid receptor agonists (MRAs), such as finerenone, compete for the binding sites of aldosterone and effectively decrease blood pressure and aldosterone-mediated gene transcription. Both approaches have been shown to be useful in treating aldosterone-mediated hypertension and vascular disease. Aldosterone synthesis, green; cortisol synthesis, red; anti-aldosterone drugs, blue.

MR, and no effect on the L-type calcium channel[26,27] (Table). Finerenone was designed to have greater cardiac activity than the available steroidal MRAs to improve myocardial function without adversely affecting sodium-potassium homeostasis in the kidney. In preclinical models of hypertension-related HF and renal dysfunction, finerenone resulted in greater cardiorenal target organ protection than steroidal MRAs.[28]

The mineralocorticoid receptor antagonist tolerability study (ARTS) was designed to assess the safety and tolerability of finerenone in patients with HF with reduced ejection fraction and mild or moderate chronic kidney disease and to select doses for phase III clinical trials.[29,30] ARTS (ClinicalTrials.gov: NCT01345656) is a multicenter, randomized, double-blind, parallel-group study divided into 2 parts: Part A tested the effects of finerenone (2.5, 5, or 10 mg once daily) in 65 patients with HF with reduced ejection fraction and mild chronic kidney disease (estimated glomerular filtration rate 60–90 mL/min/1.73 m^2); Part B compared finerenone (2.5, 5, or 10 mg daily or 5 mg twice daily) with placebo or open-label spironolactone (25 or 50 mg daily) in 392 patients with HF with reduced ejection fraction and moderate chronic kidney disease (estimated glomerular filtration rate 30–60 mL/min/1.73 m^2).[30] Finerenone 5 to 10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in decreasing biomarkers of hemodynamic stress (B-type natriuretic peptide [BNP] and amino-terminal proBNP) and albuminuria and was associated with lower incidences of hyperkalemia and worsening renal function. Adverse effects were infrequent and mostly mild. Finerenone may, therefore, offer target-organ protection with a reduced risk of electrolyte disturbances in HF patients. Finerenone is currently under investigation in 2 phase IIb clinical trials: (1) in patients with worsening chronic HF and type 2 diabetes mellitus and chronic kidney disease (ARTS-HF; ClinicalTrials.gov: NCT01807221) and (2) in patients with type 2 diabetes mellitus and diabetic nephropathy (ARTS-DN; ClinicalTrials.gov: NCT01874431).

Aldosterone Synthase Inhibitors

Although MRAs lower BP and protect against hypertension-related target organ damage, they can cause reactive increases in components of the renin–angiotensin–aldosterone system, particularly aldosterone, thus blunting their effectiveness.[12,13] Further, they do not block, and may even enhance, the non-genomic effects of aldosterone, which include stimulation of cardiac and vascular contractility, worsening of glucose homeostasis, and increasing central sympathetic drive.[31–33] Awareness of the limitations of MRAs has led to the development of a new class of anti-aldosterone agents, the selective aldosterone synthase inhibitors.[22,34,35] LCI699, the first orally active aldosterone synthase inhibitor to be developed for human use, is similar in structure to FAD286, the dextroenantiomer of the nonsteroidal aromatase inhibitor fadrozole[36] (Table). LCI699 dose-dependently decreases plasma and urine aldosterone concentrations, increases plasma renin activity, and prevents target organ damage in animal models of hypertension and HF.[37,38] Similar effects on aldosterone and renin levels have been seen in healthy humans[39] and in hypertensive patients.[12,40–43]

Table. New Drugs for Hypertension

Drug	Mechanism of Action	Status
BAY 94–8862 (finerenone)	Mineralocorticoid receptor antagonist	Phase IIb
LCI699	Aldosterone synthase inhibitor	Phase II trials*
C21	AT2 receptor agonist	Preclinical
XNT	ACE2 activator	Preclinical*
DIZE	ACE2 activator	Preclinical*
rhACE2	ACE2 activator	Phase I
HP-β-CD/Ang1-7	Ang1-7 analog	Preclinical
AVE0991	Nonpeptide agonist of MAS	Preclinical
CGEN-856S	Peptide agonist of MAS	Preclinical
Alamandine/HPβCD	Mas-related G-protein coupled receptor, member D agonist	Preclinical
PC18	Aminopeptidase N inhibitor	Preclinical
RB150 (QGC001)	Aminopeptidase A inhibitor	Phase I
LCZ696	Dual-acting angiotensin receptor-neprilysin inhibitor	Phase III
SLV-306 (Daglutril)	Dual acting endothelin-converting enzymes-neprilysin inhibitor	Phase II
PL-3994	Natriuretic peptide A agonist	Phase II
C-ANP$_{4-23}$	ANP analog, selective for NPR-C	Preclinical
AR9281	Soluble epoxide hydrolase inhibitors	Phase II*
Vasomera (PB1046)	Vasoactive intestinal peptide receptor 2 (VPAC2) agonist	Phase II
AZD1722 (Tenapanor)	Intestinal Na^+/H^+ exchanger 3 inhibitor	Phase I
Etamicastat	Dopamine β-hydroxylase inhibitor	Phase I
Vaccines		
CYT006-AngQβ	Vaccine against angiotensin II	Phase II
AngII-KLH	Vaccine against angiotensin II	Preclinical
pHAV-4AngIIs	Vaccine against angiotensin II	Preclinical
ATRQβ-001	Vaccine against angiotensin II type 1 receptor	Preclinical
ATR12181	Vaccine against angiotensin II type 1 receptor	Preclinical
Preeclampsia drugs		
DIF	Anti-digoxin antibody fragment	Phase II expedited
ATryn	Recombinant antithrombin	Phase III

ANP indicates atrial natriuretic peptide ATR, Angiotensin II type 1 receptors; DIF, Digoxin-immune Fab; KLH, keyhole limpet hemocyanin; and rhACE2, recombinant human ACE2.

*Stopped.

Four phase II studies of LCI699 have been performed in hypertensive patients.[12,40–43] The first proof-of-concept study compared LCI699 to placebo in 14 patients with primary aldosteronism.[40] LCI699 normalized plasma aldosterone and potassium but also increased 11-deoxycorticosterone and adrenocorticotropin levels and produced only modest reduction (4.2 mm Hg) in 24-hour ambulatory systolic BP. The first randomized, double-blind, placebo-controlled trial of LCI699, performed in 524 patients with primary hypertension, compared the efficacy and safety of different doses of LCI699 with eplerenone.[41] All doses of LCI699 produced significant reductions in office systolic BP that were noninferior to those seen with eplerenone. Plasma aldosterone levels were suppressed with LCI699 and increased with eplerenone; both agents were well tolerated, but adrenocorticotropin-stimulated cortisol release was blunted in ≈ 20% of the LCI699 group, likely as a result of inhibition of CYP11B1.

A subsequent study evaluated the effect of LCI699 on the cortisol response to adrenocorticotropin stimulation in 63 treated hypertensive patients to find the maximally tolerated dose in this patient population.[42] LCI699 had a dose- and time-dependent inhibitory effect on both aldosterone- and adrenocorticotropin-stimulated cortisol synthesis, consistent with inhibition of 11-β-hydroxylase (CYP11B1) activity. A fourth study evaluated the safety and efficacy of LCI699, compared with placebo and eplerenone, as add-on therapy in patients with resistant hypertension.[43] BP lowering effects of LCI699 were inferior to those of eplerenone and plasma 11-deoxycorticosterone levels increased, confirming inhibition of 11β-hydroxylase and compensatory stimulation of adrenal steroidogenesis. The nonselectivity of LCI699 resulted in off-target inhibition of the 11β-hydroxylase activity of CYP11B1, thus stimulating the hypothalamic–pituitary–adrenal feedback axis and increasing adrenocorticotropin levels and adrenal steroidogenesis to compensate for the reduced cortisol secretion.[12] In the setting of aldosterone synthase (CYP11B2) inhibition, this resulted in up to a 10-fold increase in the biologically active aldosterone synthase substrate, 11-deoxycorticosterone,

which could activate the MR. These effects could account for the disappointing BP reductions seen at higher doses and with twice daily administration of LCI699.

Based on the results of the phase II trials, further development of LCI699 was discontinued, and the investigators outlined the mechanistic properties that would be required for a therapeutically successful aldosterone synthase inhibitor: (1) greater selectivity for aldosterone synthase inhibition on CYP11B2 over 11β-hydroxylase inhibition on CYP11B1; (2) a longer plasma elimination half-life than LCI699; and (3) preferential inhibition of the 18-oxidase step of aldosterone synthesis, thus preventing conversion of the weak mineralocorticoids 18-OH corticosterone and corticosterone to aldosterone.[12] A series of novel pyridyl- or isoquinolinyl-substituted indolines and indoles have recently been synthesized using a ligand-based approach. These compounds are as potent and more selective than LCI699 for CYP11B2 over CYP11B1[14,44] and are currently being tested as treatments for mineralocorticoid-dependent CVD and renal disease.

Activators of the Angiotensin-Converting Enzyme2/Angiotensin(1–7)/MAS Receptor Axis

The classical renin–angiotensin system (RAS) has been studied extensively for decades[45] and has yielded numerous effective therapies for hypertension and its complications. More recently, components of the RAS that play counterregulatory roles have been identified, characterized and put forward as therapeutic targets for hypertension and other forms of CVD[46–50] (Figure 2). The carboxypeptidase angiotensin-converting enzyme 2 (ACE2) converts the decapeptide angiotensin I (Ang I) to the Ang(1–9) nonapeptide and the octapeptide Ang II to the Ang(1–7) heptapeptide. Ang(1–7) has been studied intensively and shown to activate the G-protein-coupled Mas receptor, triggering a signaling cascade that results in vasodilation, reduction in oxidative stress, and antihypertrophic and antifibrotic effects. ACE2 also mediates degradation of Ang II, likely contributing to the antihypertensive/vasoprotective effects of the counterregulatory RAS pathway.

Amplification of ACE2/Ang(1–7)/Mas signaling opposes the effects of the classical RAS and lowers BP and prevents or reverses related target organ damage in hypertensive animal models.[48] Interestingly, inhibitors of the classical RAS, including ACE inhibitors and angiotensin receptor blockers (ARBs), increase circulating Ang(1–7) levels, and the Mas antagonist A-779 attenuates the effects of the ACE inhibitors and ARBs, indicating that the 2 RAS axes interact[49] and provide further evidence for the therapeutic potential of the ACE2/Ang(1–7)/Mas axis in hypertension.

The more recently described Ang(1–9) has been shown to lower BP and reverse/ameliorate cardiovascular injury in animal models of hypertension by a mechanism that involves activation of the angiotensin type 2 receptor.[51] Unlike Ang(1–7), Ang(1–9) does not activate the Mas receptor. The therapeutic potential of angiotensin type 2 receptor activation is being

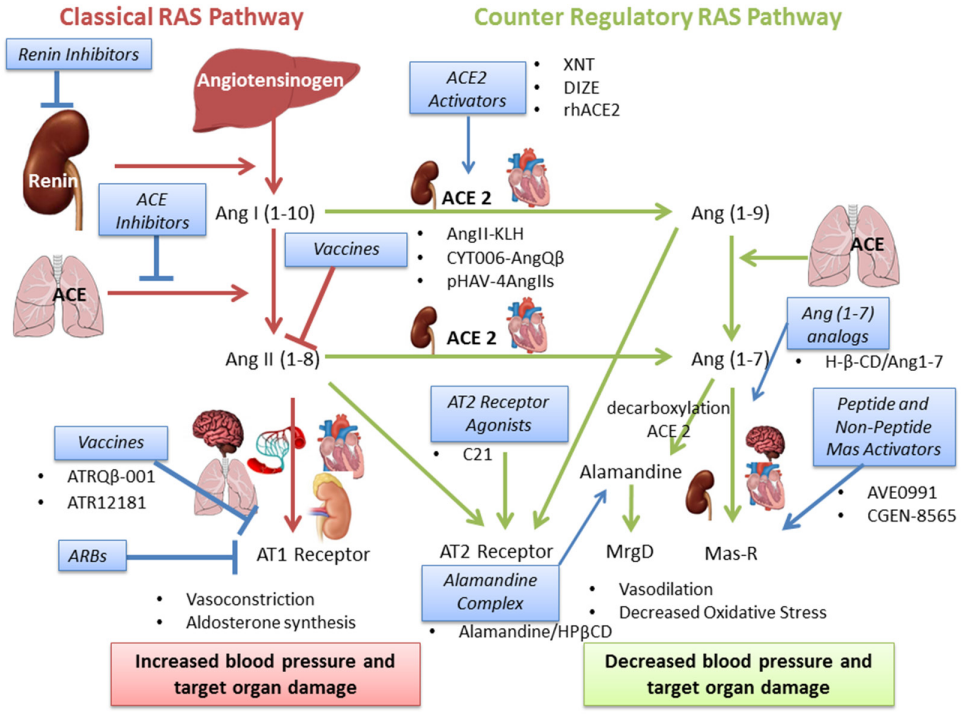


Figure 2. Drugs targeting the classical and counter regulatory renin angiotensin systems (RAS). Activation of the classical RAS pathway increases BP and target organ damage, and this pathway is the target for many currently available antihypertensive drugs, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Novel approaches to RAS inhibition, including vaccines targeting angiotensin II (Ang II) and the angiotensin II type 1 (AT1) receptor, are being evaluated in preclinical and clinical trials. In contrast, activation of the more recently described counter regulatory RAS pathway decreases blood pressure (BP) and target organ damage, and drugs that activate this pathway are beginning to be developed as antihypertensive agents. These include ACE2 activators, Ang (1–7) analogs, AT2 receptor agonists, peptide and nonpeptide activators of the Mas receptor, and alamandine complexed with cyclodextrin. Classical RAS, red; counter regulatory RAS, green; drugs, blue. ATR indicates AT1 receptor; MrgD, Mas-related G-protein-coupled receptor, member D; and rhACE2, recombinant human ACE2.

explored in preclinical studies. A selective nonpeptide angiotensin type 2 receptor agonist, compound 21(C21), has been found to have anti-inflammatory, antifibrotic and antiapoptotic properties, but not to lower BP[47] (Table). These findings suggest that C21 may be useful in preventing hypertension-induced target organ damage.

Interest in ACE2 as a therapeutic target has led to the synthesis of small molecule ACE2 activators, including XNT[52] and DIZE,[53] which lower BP, improve myocardial function, and reverse myocardial and perivascular fibrosis in the spontaneously hypertensive rat (SHR; Table). Activation of ACE2 also decreases monocrotaline-induced pulmonary hypertension by a mechanism that involves Mas activation.[54,55] As an alternative to pharmacological ACE2 activation, recombinant human ACE2 (rhACE2) has been shown to lower BP in SHR, to have anti-inflammatory effects in a model of lipopolysaccharide-induced lung injury,[56] and to slow the progression of diabetic nephropathy in animal models[57] (Table). A phase I study in healthy volunteers demonstrated sustained (>24 h) suppression of circulating Ang II levels after a single intravenous injection of rhACE2 with no effect on BP and no major adverse effects.[58]

Ang(1–7) has been administered in phase I/II studies as a putative antiproliferative and antiangiogenic agent to patients with advanced cancers refractory to standard therapy and as a hematopoietic agent to patients with multilineage cytopenias following chemotherapy.[59,60] These studies were limited in scope, and native Ang(1–7) has not been developed further because of its abbreviated half-life in vivo. A cyclic Ang(1–7) analog containing a thioether bridge that makes it resistant to enzymatic digestion and a hydroxypropyl-β-cyclodextrin incorporated Ang(1–7) formulation (HP-β-CD/Ang1-7) have been synthesized and shown to be cardioprotective in animal models of myocardial infarction and insulin resistance/type 2 diabetes[61–63] (Table).

As an alternative to Ang(1–7), nonpeptide agonists of the Mas receptor, for example, the imidazole compound AVE0991,[64] and novel G-protein-coupled receptor activating peptides, for example, CGEN-856S that have high specificity for the Mas receptor,[65] have been shown to lower BP and protect the vasculature and kidneys in animal models of hypertension and CVD (Table). The relative merits of Mas receptor activation versus ACE2 stimulation are being debated, but all agree that randomized controlled trials in humans with hypertension and related CVDs are needed to assess the therapeutic potential of activating the ACE2/Ang(1–7)/Mas receptor axis.[46,48]

A novel member of the Ang peptide family, Ala^1-Ang(1–7) (alamandine), has been isolated from human plasma and rat heart.[50,66] Alamandine is a product of decarboxylation of the N-terminal Asp residue of Ang II to form Ala, which has been demonstrated in heart, followed by hydrolysis of Ala^1-Ang II by ACE2. Alamandine is similar in structure to Ang(1–7) except for replacement of the N-terminal Asp residue by Ala. It has antihypertensive, antifibrotic, and central cardiovascular effects similar to those reported for Ang(1–7), but acts through a different receptor, the Mas-related G-protein-coupled receptor, member D. Alamandine incorporated into a β-cyclodextrin inclusion complex (alamandine/HPβCD) has been shown to be orally active and to reduce BP in SHR and inhibit cardiac fibrosis in isoproterenol-treated rats[66] (Table). The oral bioavailability of alamandine/HPβCD has revived prospects for exploring the therapeutic potential of Ang(1–7)-related peptides.

Centrally Acting Aminopeptidase Inhibitors

Activation of the brain RAS plays an important role in the pathogenesis of hypertension in animal models.[67,68] Two membrane-bound zinc metalloproteases, aminopeptidase A (APA) and aminopeptidase N, are involved in the metabolism of brain Ang II and III, respectively (Figure 3). APA cleaves the N-terminal Asp from Ang II to form Ang III, and aminopeptidase N cleaves the N-terminal Arg from Ang III to form Ang IV. Ang II and Ang III have similar affinities for Ang II receptors and both peptides stimulate pressor responses by activating sympathetic nervous system activity, inhibiting the baroreflex at the level of the nucleus tractus solitarius and increasing release of arginine vasopressin into the circulation. Studies using selective APA (EC33) and aminopeptidase N (PC18) inhibitors have demonstrated that brain Ang III (not Ang II, as in the periphery) plays a predominant role in BP control in animal models and have identified APA as a potential therapeutic target for the treatment of hypertension[68–71] (Table).

Orally administered RB150, a dimer of EC33, has been shown to enter the brain of SHR and DOCA (deoxycorticosterone acetate)-salt rats to inhibit brain APA activity and block the formation of Ang III and to normalize BP for several hours[68,70,71] (Table). The RB150-induced depressor response was related to inhibition of arginine vasopressin release, resulting in a diuresis and reduction in volume, and a decrease in sympathetic tone, resulting in reduced vascular resistance. Systemic RAS activity was unaffected, and systemic administration of an ACE inhibitor potentiated the RB150-induced BP decrease, suggesting that centrally acting APA inhibitors might be used in combination with systemic RAS blockers to improve BP control and reduce cardiovascular disease risk in hypertensive patients.[70]

RB150 (renamed QGC001) has been administered in ascending doses (10–1250 mg) to 56 healthy male volunteers.[72] QGC001 did not significantly change heart rate or BP at any dose and was safe and well tolerated in this phase Ia study, as well as in a phase Ib study where it was administered in single doses of ≤2000 mg and in multiple doses over a 7 day period.[68] A proof-of-concept exploratory study is planned to evaluate the clinical efficacy of RB150/QGC001 for treating hypertension in humans.

Vasopeptidase Inhibitors

The zinc metalloprotease neprilysin (neutral endopeptidase 24.11) is a therapeutic target for hypertension and other forms of CVD because it degrades the natriuretic peptides atrial natriuretic peptide (ANP), BNP, and urodilatin,[73] and the increase in circulating natriuretic peptide levels that results from neprilysin inhibition leads to natriuresis, vasodilation, renin–angiotensin–aldosterone system inhibition, reduced sympathetic drive, and antiproliferative and antihypertrophic effects

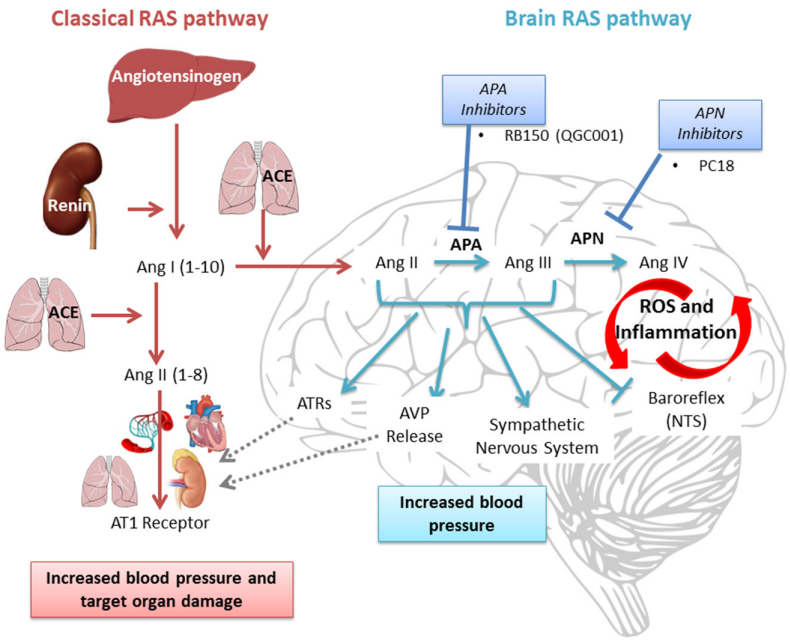


Figure 3. The brain renin angiotensin system (RAS) pathway. Activation of the brain RAS in response to oxidative stress and inflammation increases sympathetic nervous system outflow and arginine vasopressin (AVP) release and inhibits the baroflex, thus raising BP. Angiotensin (Ang) III, which is generated from Ang II by aminopeptidase A (APA), is the predominant pressor peptide in brain in animal models, and APA is a therapeutic target for treatment of hypertension. The APA inhibitor RB150 (QGC 001) has been shown to pass the blood–brain barrier and lower BP in animal models; exploratory studies are underway in humans. Red, classical RAS; light blue, brain RAS pathway; blue, drugs, dotted arrows indicate crosstalk between the systems. APN indicates aminopeptidase N; AT1, angiotensin II type 1; ATR, AT1 receptor; and ROS, reactive oxygen species.

on the heart and vasculature[74] (Figure 4). However, neprilysin inhibitors are ineffective in lowering BP, likely because neprilysin also degrades vasoconstrictor peptides, for example, Ang II and endothelin-1.[75,76] Thus, combining a neprilysin inhibitor with an RAS blocker or an endothelin-converting enzyme inhibitor offers the theoretical advantage of enhancing the favorable vasodilator/natriuretic effects of ANP and BNP and reducing the deleterious vasoconstrictor effects of Ang II or endothelin-1 on BP and target organ damage.

Dual-Acting Angiotensin Receptor–Neprilysin Inhibitors

The first-in-class angiotensin receptor–neprilysin inhibitor LCZ696 is a novel single molecule composed of the neprilysin inhibitor prodrug AHU377 (sacubitril) and the ARB valsartan in a 1:1 ratio[77] (Figure 4; Table). In a proof-of-concept randomized, double-blind, placebo-controlled, active comparator trial, graded doses of LCZ696 were compared with graded doses of valsartan and to AHU377 in 1328 patients with mild-to-moderate hypertension.[78] LCZ696 produced significantly greater reductions than valsartan in office systolic and diastolic BP and 24-hour ambulatory systolic BP and pulse pressure over the entire dose range tested; AHU377 produced a BP reduction significantly greater than placebo but smaller than either LCZ696 or valsartan. Plasma ANP and cyclic guanosine monophosphate (second messenger for neprilysin activity) levels increased with LCZ696, but the changes in biomarker levels were poorly correlated with BP responses. There were no cases of angioedema, but the trial included only 8% black patients, a group prone to develop angioedema when treated with a combined ACE–neprilysin inhibitor,[79] and 3% Asians. To address the lack of information about the efficacy and safety of LCZ696 in Asian persons, a randomized, double-blind, placebo-controlled study was performed in 589 hypertensive patients in 5 Asian countries (Japan, China, Korea, Taiwan, and Thailand).[80] Reductions in systolic BP in clinic and nighttime ambulatory settings were 6 to 8 mm Hg greater than those previously reported for Western patients.[78] This was attributed to the natriuretic effect of neprilysin inhibition, as valsartan monotherapy has been shown to be relatively ineffective in controlling nighttime BP in Japanese patients.[81] No cases of angioedema or other serious adverse effects were noted. The authors pointed out the potential benefit of this BP lowering effect in prevention of stroke in Asian populations.

In light of its modest BP lowering effects in Western populations, LCZ696 is currently under development for treatment of HF, resistant hypertension, and systolic hypertension in the elderly, conditions that are mediated by a combination of vasoconstriction, volume overload, and neurohormonal activation. A Phase II double-blind randomized controlled trial (PARAMOUNT) compared the effects of LCZ696 to those of valsartan alone in 301 patients with HF with preserved ejection fraction.[82] LCZ696 induced a greater reduction in systolic BP (9 mm Hg) than valsartan (3 mm Hg), but the changes in biomarkers (NT-proBNP), left atrial volume, renal function, and functional class were independent of the BP lowering effect of LCZ696.[83] However, since BP was controlled in the majority of participants at the time of enrollment in PARAMOUNT, a BP-dependent effect of LCZ696 may have been seen in a different population with higher baseline BP.

The Phase III Prospective Comparison of angiotensin receptor–neprilysin inhibitor with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial was a randomized double-blind trial that compared the effects of LCZ696 (200 mg twice daily) to enalapril (10 mg twice daily) in 8442 patients with class II, III, or IV HF and an ejection fraction ≤40%.[84,85] The primary outcome was a composite of death from cardiovascular cause or hospitalization for HF. The trial was stopped early (median follow-up 27 months) because of overwhelming benefit. There was a 20% reduction in cardiac death, a 16% reduction in total mortality and a 21% reduction in hospitalization for HF, all highly significant, in the LCZ696 arm compared to the enalapril arm. Further, the symptoms and physical

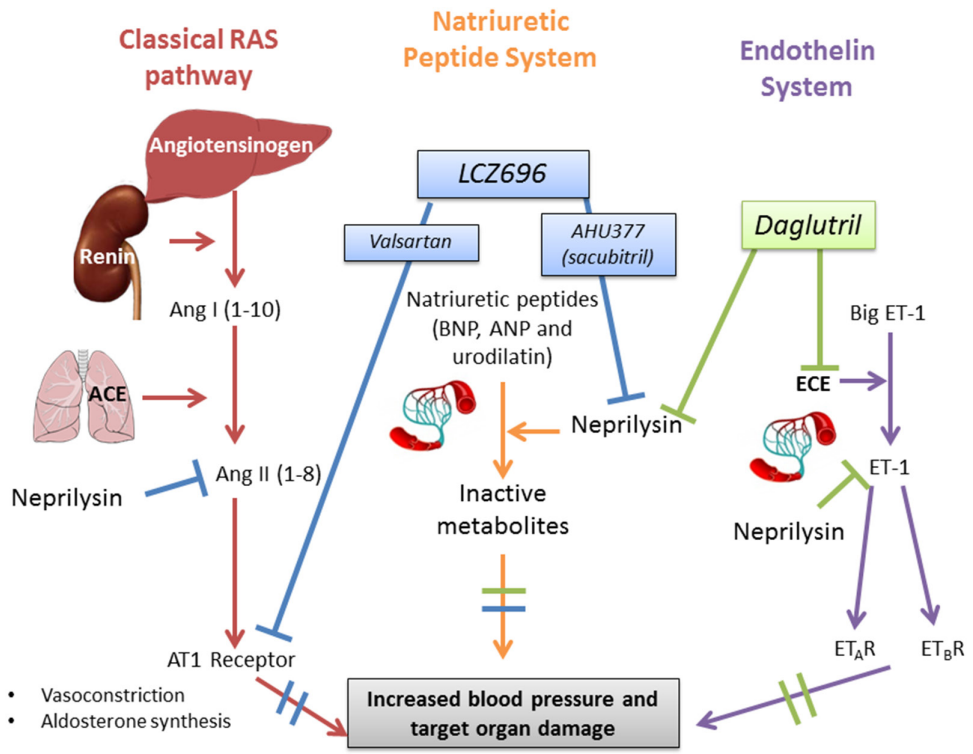


Figure 4. Vasopeptidase inhibitors. Combining an inhibitor of the natriuretic peptide degrading enzyme neprilysin with an angiotensin receptor blocker (ARB) or an endothelin converting enzyme (ECE) inhibitor in the same molecule offers the theoretical advantage of enhancing the favorable vasodilator/natruiretic effects of the natriuretic peptides and reducing the deleterious vasoconstrictor/proinflammatory effects of angiotensin II (Ang II) and endothelin-1 (ET-1) on blood pressure (BP) and target organ damage. The ARB–neprilysin inhibitor (ARNI), LCZ696, is a single molecule comprising the ARB valsartan and the neprilysin inhibitor pro-drug AHU377 (sacubitril). LCZ696 has been shown to lower BP, particularly in Asian populations, and to prevent death from cardiovascular (CV) causes and hospitalization for heart failure (HF) in patients with reduced left ventricular ejection fraction (LVEF). The ECE–neprilysin inhibitor dagutril has been shown to lower BP in patients with type 2 diabetes mellitus and nephropathy and to reduce pulmonary arterial pressure in patients with HF. Red, classical RAS; orange, natriuretic peptide system; purple, endothelin system; blue, LCZ696; green, dagutril.

limitations of HF were reduced with LCZ696. Mean systolic BP was slightly but significantly (3.2 mm Hg, $P<0.001$) lower in the LCZ696 group, but this did not account for the outcome benefit. Safety concerns were minor: the LCZ696 group had more symptomatic hypotension, but this rarely required discontinuation of treatment, and more participants in the enalapril group stopped treatment because of other adverse events (most commonly cough or elevated serum potassium) or renal impairment. Angioedema was uncommon in both treatment groups, and the few cases that occurred did not cause airway compromise. However, the study had a run-in phase that excluded persons who were intolerant of an ACE inhibitor or ARB and enrolled few black patients, a group prone to develop angioedema in response to dual vasopeptidase blockade.[79] Despite these caveats, the PARADIGM-HF trial has been hailed as revealing the first significant advance in HF therapy in nearly a decade and as offering new thresholds of hope for patients with chronic HF.[86]

The ongoing prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker measuring arterial stiffness in the elderly (PARAMETER) study (EUDract ID:2012-002899-14; ClinicalTrials.gov: NCT01692301) compares the effects of LCZ696 versus the ARB olmesartan on aortic stiffness and central aortic hemodynamics in older (aged ≥60 years) patients with systolic hypertension.[87] The central hypothesis of PARAMETER is that by simultaneously enhancing natriuretic peptide effects and inhibiting the RAS, LCZ696 will reduce aortic stiffness and characteristic impedance and improve central hemodynamics, perhaps via mechanisms that are independent of BP reduction. This concept will be examined in greater depth in a parallel study that will determine aortic distensability by MRI and retinal vascular remodeling by scanning laser Doppler flowmetry, respectively (www.ClinicalTrials.gov: NCT01870739). A novel aspect of both studies is assessment of mean aortic pressure and pulse wave velocity on a 24-hour basis using a novel cuff-based oscillometric ambulatory BP monitoring device.[88]

Dual-Acting Endothelin Converting Enzyme–Neprilysin Inhibitors

Orally active dual inhibitors of neprilysin and endothelin-converting enzyme have been developed, and one of these (daglutril, SLV-306) has been studied in rodent models of diabetes mellitus and in patients with hypertension, HF, and type 2 diabetes mellitus[89–93] (Figure 4; Table). Daglutril is a prodrug that is hydrolyzed after oral administration to the active metabolite KC-12615, a mixed inhibitor of neprilysin and endothelin-converting enzyme.[89] In diabetic rat models, daglutril and a similar compound have been shown to reduce

BP and proteinuria and prevent nephrosclerosis as effectively as the ACE inhibitor captopril.[90,94] Daglutril has also been shown to be safe and well tolerated in healthy volunteers,[92,95] and biomarker measurements confirmed dual suppression of neprilysin and endothelin-converting enzyme activity in these subjects.[92] Data from a multicenter, randomized controlled trial performed in 75 patients with HF showed that daglutril reduced pulmonary and right atrial pressures without affecting systemic arterial pressure, cardiac output, or heart rate.[89] Daglutril has also been shown in a small randomized, double-blind, placebo-controlled crossover trial to lower BP but not to reduce albuminuria in patients with type 2 diabetes mellitus and nephropathy.[93]

Natriuretic Peptide Receptor Agonists

Natriuretic peptide receptor agonists are being developed as an alternative approach to inhibiting the degradation of endogenous natriuretic peptides for the treatment of HF and refractory or resistant hypertension. The natriuretic peptide receptor A (NPR-A) agonist PL-3994 is a synthetic molecule that contains an amino acid mimetic and has reduced affinity for the natriuretic peptide clearance receptor (NPR-C) and increased resistance to neprilysin, resulting in a prolonged half-life after subcutaneous administration[96] (Table). A phase I trial of a single subcutaneous dose of PL-3994 in healthy volunteers showed increased natriuresis and diuresis, elevation in plasma cyclic guanosine monophosphate levels, and reduction in systemic BP compared with placebo. A phase II trial in volunteers with hypertension who were receiving ≥1 antihypertensive medications demonstrated a reduction in systemic BP compared with placebo. In particular, PL-3994 appeared to act synergistically with ACE inhibitors, suggesting that it could be administered as an adjunct to standard therapy in patients with refractory or resistant hypertension or HF. No safety concerns were raised in either trial (ClinicalTrials.gov: NCT00686803).

C-ANP$_{4\text{-}23}$ is a ring deleted analog of ANP that is selective for NPR-C and decreases the enhanced expression of Giα proteins that has been implicated in the pathogenesis of hypertension in animal models[97] (Table). Intraperitoneal injection of C-ANP$_{4\text{-}23}$ has been shown to decrease BP in SHR by inhibiting enhanced expression of Giα proteins and reducing nitro-oxidative stress, not by modulating the eNOS/cyclic guanosine monophosphate pathway. This study revealed a novel function of NPR-C, which has generally been considered a clearance receptor for natriuretic peptides and has raised the possibility that NPR-C agonists, such as C-ANP$_{4\text{-}23}$, could be useful for the treatment of hypertension and related CVDs.

Soluble Epoxide Hydrolase Inhibitors

Soluble epoxide hydrolase (s-EH) catalyzes the conversion of multiple lipid epoxides to the corresponding dihydroxy lipids.[98] Substrates of s-EH include members of the arachidonic acid family, for example, epoxyeicosatrieonic acids, and the effects of s-EH inhibitors have been attributed to increased epoxyeicosatrieonic acid levels.[99] Preclinical studies have shown that inhibitors of s-EH lower BP, prevent and reverse pressure overload–induced cardiac hypertrophy, attenuate ischemic and ischemia-reperfusion injury of the brain and heart, prevent atherosclerosis and aneurysm formation, and attenuate insulin resistance in animal models.[98–100]

AR9281 is a potent and selective inhibitor of human s-EH that has been shown to lower BP, improve vascular function, and reduce renal damage in a rat model of Ang II-induced hypertension[101] and to improve glycemic parameters in a mouse model of diet-induced obesity[102] (Table). The metabolic effects of AR9281 were absent in mice with diet-induced obesity due to deletion of the *Ephx2* gene, which encodes s-EH, validating the mechanism of the AR9281 effect. Randomized double-blind, placebo-controlled studies in healthy volunteers have shown that AR9281 dose-dependently inhibits s-EH at doses that are well tolerated.[103] A randomized double-blind, placebo-controlled dose-ranging phase II study in patients with mild to moderate hypertension and impaired glucose tolerance was terminated in November 2009, and no efficacy results have been reported, suggesting that it was ineffective in lowering BP[104] (ClinicalTrials.gov: NCT00847899). However, s-EH inhibitors have other promising therapeutic applications, for example, inflammation, pain, and CVD that warrant future investigation.[105]

Vasoactive Intestinal Peptide Receptor Agonist

Vasoactive intestinal peptide (VIP) is a neuropeptide with vasodilator and positive inotropic/chronotropic properties that are mediated via the G-protein-coupled receptors VPAC1 and VPAC 2.[106] Deficiency in VIP and alterations in properties of VPAC1 and 2 have been described in various forms of cardiopulmonary disease, and VIP is a therapeutic target for hypertension, both systemic and pulmonary, as well as HF. To overcome the abbreviated half-life (<2 min) of VIP, vasomera (PB1046), a stable long-acting form of VIP that is selective for VPAC2, has been developed by fusing an analogue of VIP with an elastin-like polypeptide[107] (Table). Selectivity for VPAC2 reduces the potential gastrointestinal side effects associated with activation of VPAC1. Vasomera reduces BP and improves inotropic and lusitropic properties of the heart in animal models of hypertension and HF and has been shown to be safe and well-tolerated after single subcutaneous or intravenous injections in phase I studies in patients with essential hypertension (ClinicalTrials.gov: NCT01523067, NCT01873885). The pharmacodynamic activity of subcutaneous vasomera is supportive of a once weekly dosing regimen that could allow for chronic use in the home setting. Intravenous dosing of vasomera is being evaluated for short-term treatment of HF in the hospital setting.

Intestinal Na^+/H^+ Exchanger 3 Inhibitor

Excessive sodium intake and impaired sodium excretion plays an important role in the pathogenesis of hypertension and its complications, including HF and chronic kidney disease. Electroneutral Na^+/H^+ exchangers, for example, NHE2, NHE3, and NHE8, that are expressed in the apical regions of the enterocyte transport sodium from the intestinal lumen into enterocytes.[108,109] NHE3 (SLC9A3), the major contributor to intestinal sodium uptake, is inhibited selectively by tenapanor, a compound that does not cross the intestinal barrier (Table). Orally administered tenapanor decreases urinary sodium excretion and increases stool sodium in humans and reverses

extracellular volume expansion, lowers BP, and reduces albuminuria and cardiac and renal injury in the 5/6 nephrectomy rat model of sodium-dependent hypertension. Tenapanor also enhances the BP lowering and organ protective effects of the ACE inhibitor enalapril in this model. These findings suggest that reducing sodium transport in the gut could provide a useful alternative or adjunct to dietary sodium reduction or diuretics in the treatment of hypertension and related target organ damage.

Dopamine β-hydroxylase (DβH) Inhibitor

Dopamine β-hydroxylase (DβH), the enzyme that catalyzes the hydroxylation of dopamine to form noradrenaline in the sympathetic nervous system, is a therapeutic target for treatment of hypertension and other cardiovascular disorders characterized by sympathetic activation, for example, HF.[110] Inhibition of DβH offers theoretical advantages over adrenergic receptor blockade: (1) it causes gradual sympathetic slowdown instead of acute inhibition and (2) it increases dopamine availability, thus causing renal vasodilation, natriuresis, and diuresis. First, second, and early third generations DβH inhibitors, for example, disulfiram, fusaric acid, and nepicastat, either lacked potency or selectivity for DβH or caused severe CNS-related adverse effects and thus were not clinically useful. Etamicastat (BIA 5–453) is a potent and reversible inhibitor of DβH that does not pass the blood brain barrier and thus is selective for peripheral DβH when administered orally (Table).[111] Etamicastat lowers BP in the SHR, but not in normotensive WKY (Wistar Kyoto) rats, and prolongs survival in animal models of HF.[112] Studies in healthy men and men with mild to moderate hypertension showed good tolerability and statistically significant dose-dependent decreases in 24-h ambulatory blood pressure (ABP).[111] These emerging preliminary results warrant further testing in broader populations.

Vaccines

Vaccines targeting renin for the purpose of treating hypertension have been available for over 50 years.[113] Although a renin vaccine successfully lowered BP in animal models, it induced autoimmune disease of the kidneys and further development was suspended.[114] An Ang I vaccine also lowered BP in animal models,[115,116] but was ineffective in a randomized, double-blind, placebo-controlled clinical trial.[117] Further, a vaccine raised in response to an Ang II–derived peptide conjugated to a virus-like particle derived from the bacteriophage Qβ (AngQb) was effective in producing anti-Ang II antibodies and reducing BP in SHR, despite increasing circulating Ang II levels[118] (Figure 2; Table). In a placebo-controlled, randomized phase I trial, 12 healthy volunteers received a single injection of AngQb.[118] Ang II–specific antibodies were raised in all subjects, and the AngQb antigen was well tolerated.

A subsequent double-blind, randomized, placebo-controlled phase IIa trial tested the effects of immunization with 2 doses of AngQb (also named CYT006-AngQb) on ambulatory BP in 72 patients with mild-to-moderate hypertension.[119] Mean ambulatory daytime BP and the early morning BP surge were reduced significantly (by 9/4 and 25/13 mm Hg, respectively) in the high dose group. Changes from baseline in nighttime BP were not significantly different from placebo in either group, and the diurnal pattern of BP response to the vaccine paralleled the diurnal rhythm of RAS activity, with higher levels in daytime than nighttime, and the highest levels of all during the early morning surge in BP. Most observed adverse events were not serious and similar to those seen with other vaccines, that is, mild, transient reactions at the injection site and influenza-like symptoms. The induced antibody response was reversible, with a half-life of ≈4 months, a time course that is compatible with a treatment regimen of 3 to 4 injections per year, which could coincide with regular clinic visits for hypertension management. The authors commented that the immunization strategy could reduce the need for daily dosing of antihypertensive medications, thus enhancing adherence. However, the study was limited by inclusion of a small number of otherwise healthy hypertensive participants, and later stage clinical trials will be needed to evaluate efficacy and safety in a broader hypertensive population.

A subsequent study that used an accelerated immunization schedule in an attempt to induce higher antibody titers, and thereby, greater BP reduction was successful in boosting the antibody titer 5-fold, but resulted in smaller BP reductions.[120,121] Antibody affinities were significantly lower, and the amount of Ang II sequestered in the blood of vaccinated persons was significantly less than in the previous study.[119] Changes in daytime ambulatory BP correlated with individual antibody affinities and, in particular, with measures of off-rates (how long Ang II is bound to the antibodies). Thus, persons whose antibodies had higher affinity and bound Ang II for a longer period of time showed greater BP reductions. These findings suggest that an accelerated immunization regimen leads to antibody responses with higher titers but lower affinities, perhaps related to disruption in the β-cell antibody affinity maturation process, thereby creating a lower capacity for sequestering Ang II in the blood, resulting in less BP reduction. The authors concluded that a better understanding of how differences in dose and timing of immunizations affect antibody titers, affinities, and BP is crucial for the successful development of an effective vaccine therapy for hypertension. Ongoing phase II trials in patients with mild-to-moderate hypertension are exploring these issues.[122]

Preclinical studies are evaluating in hypertensive rodent models the safety and efficacy of vaccines against various peptide sequences within the Ang II type 1 receptor, ATRQB-001 and ATR12181,[123,124] against Ang II conjugated via the N-terminus to keyhole limpet hemocyanin[125] and against a chimeric protein (pHAV–4 Ang IIs) that presents 4 successive repeated Ang II sequences as the functional epitope on the surface of the hepatitis A virus-like particle[126] (Figure 2; Table). In all cases, significant BP reductions were achieved, keeping alive the concept that vaccine therapy might be useful in the treatment of human hypertension and its complications.

Novel Approaches to Preeclampsia Treatment

Immunologic approaches are also being explored for the treatment of preeclampsia. Endogenous digitalis-like factors (EDLFs) are a family of circulating Na/K-ATPase inhibitors, including marinobufagenin, that are elevated in preeclampsia and contribute to its pathogenesis by mediating

vasoconstriction and vascular fibrosis and inhibiting proliferation and invasion of the cytotrophoblast.[127–130] An antidigoxin antibody fragment (*Digibind*, Ovine Digoxin Immune Antibody) has been shown to attenuate the inhibitory effects of EDLFs on Na/K-ATPase, to lower BP in animal models of volume-dependent hypertension and to reduce maternal BP and preserve renal function in women with preeclampsia[131,132] (Table).

A randomized, double-blind, placebo-controlled trial, Digibond Efficacy Evaluation in Preeclampsia, demonstrated beneficial effects on renal function and a trend toward reduction in antihypertensive drug usage but no prolongation of pregnancy or improvement of maternal outcome overall in women with severe preeclampsia.[129,133] A secondary analysis of Digibond Efficacy Evaluation in Preeclampsia stratified participants by circulating levels of EDLF activity and found that the beneficial effects of Digibind on renal function and on utilization of antihypertensives, as well as some maternal and fetal/neonatal outcomes, were greater in women who were EDLF positive.[129] Digibind production was terminated by its manufacturer in 2010, and DigiFab, affinity purified Fab fragments of antidigoxin antibody, became the only antidigoxin antibody available for clinical use.[130] DigiFab has similar effects as Digibind on EDLFs derived from the blood of women with preeclampsia. Ongoing expedited phase II studies are evaluating the safety and efficacy of digoxin-immune Fab for treatment of preeclampsia (Table).

Antithrombin replacement is a novel approach for the treatment of early onset severe preeclampsia that has been shown in small uncontrolled studies to lower BP, reduce proteinuria, and improve coagulation parameters.[134] The Prospective Randomized Evaluation of the Safety and Efficacy of Recombinant Antithrombin in Very Preterm Preeclampsia (PRESERVE-1; ClinicalTrials.gov: NCT02059135) is an ongoing phase III randomized placebo controlled trial of recombinant human antithrombin (ATryn) for the treatment of early (24–28 weeks) onset preeclampsia (Table). The primary end point is the increase in gestational age from randomization to delivery; secondary end points include a large number of maternal and fetal outcomes.

Part II. Interventional Treatments

In the 2013 ESH/ESC[135] Guidelines for the Management of Arterial Hypertension, interventional strategies are mentioned as therapeutic options for severe TRH. In Part II of this Compendium Review, we focus on 2 main interventional approaches, that is, renal denervation (RDN) and baroreflex activation therapy (BAT) because these interventions are used in clinical practice in some countries. We also discuss briefly other interventional approaches to TRH.

Renal Denervation

This is a rapidly growing research field with numerous published papers dealing with RDN. In this Comprehensive Review, we have focused on clinical aspects and established catheter-based techniques of RDN, but also provide some insights into the emerging field of alternative techniques targeting renal nerves.

Increased sympathetic activity plays an important role in the development, maintenance, and acceleration of arterial hypertension,[136,137] especially in TRH. Activation of efferent sympathetic nerves to the kidney stimulates renin release, enhances tubular reabsorption of sodium and water, and decreases renal blood flow.[137] In addition, activation of afferent sensory nerves, for example, stimulated by stretch, renal ischemia, hypoxia, or other injury, increases central nervous system sympathetic outflow and, as a consequence, sympathetic activity in key organs, including the heart, kidney, and vasculature, in particular the small resistance vessels.[138,139] Catheter-based RDN has been introduced as a new interventional approach targeting sympathetic nerve activity, and hence arterial hypertension in humans.

The first nonrandomized, proof-of-concept study (Symplicity HTN-1) of RDN patients with TRH (systolic BP ≥160 mm Hg) was published in 2009.[140] There was a BP reduction of 27/17 mm Hg at 6 months of follow-up, without any significant safety issues. In the subsequent randomized controlled Symplicity HTN-2 study, a 2 week observation period was required and baseline office BP had to be ≥160 mm Hg (or ≥150 mm Hg in diabetics, respectively).[141] A BP reduction of 32/12 mm Hg was observed after RDN compared with the control group (1/0 mm Hg) with no outstanding safety concerns. Long-term data (36 months follow-up) from both studies showed that BP reduction was maintained or even became greater, suggesting that clinically meaningful reinnervation did not occur.[142,143] However, concerns about the design of the Symplicity HTN-1 and HTN-2 studies have been raised, for example, lack of 24-h ambulatory blood pressure monitoring (ABPM), to confirm true resistant hypertension, (ie, white coat effect was not definitely excluded) and the unblinded design of the studies.[144]

To overcome these deficiencies and after the advice of the Food and Drug Administration of the United States, the prospective, single-blind, randomized, sham-controlled Symplicity HTN-3 trial was performed.[145] The primary safety end point was met, but the prespecified primary efficacy end point (reduction in office BP) was not reached. There was significant BP reduction from baseline in both groups ($P<0.001$), but between the RDN and sham-control group, neither office (−2.29 mm Hg, $P=0.026$) nor 24-h ABPM (−1.96 mm Hg, $P=0.98$) was significantly different at 6 months of follow-up.[145]

After publication of the primary findings of Symplicity HTN-3, it became clear that the results are difficult to interpret because of procedural shortcomings. Post hoc analysis of the imaging taken during RDN showed that only 19 patients had complete 4 quadrant ablations (covering 360° of the renal artery) for both renal arteries and only 68 for one renal artery, respectively.[146] These data indicate that 253 of the participants randomized to the active treatment arm of the study did not have circumferential ablation of both renal arteries, calling into question the completeness of RDN in the trial. Office systolic BP changes in the group with incomplete RDN of both renal arteries were −14.2±24 (N=253); in those with ≥1 complete RDN, −16.1±23 (N=68); and in those with complete RDN of both arteries, −24.3±23 mm Hg (N=19). In addition, 60 of the 111 operators performed just 1 or 2 RDN

procedures, further questioning the quality of the RDN procedures in the trial.[146] Although each procedure was supervised by an experienced proctor and performed per protocol instructions, the denervation achieved was thus incomplete in most cases, owing to an insufficient number of ablations, lack of 4-quadrant ablations, or other technical features that might explain the failure to lower BP significantly.[147]

In contrast to previous trials, mainly conducted in Europe and Australia, approximately one-quarter of patients enrolled in the Symplicity HTN-3 study were African American and there appeared to be an interaction with race and change in office BP (*P* for interaction =0.09). In African Americans, office systolic BP decreased by 15.5 in the RDN group and 17.8 mm Hg in the control group (*P*=0.641). In Non-African Americans (nearly all were white), office systolic BP was reduced by 15.2±24 mm Hg in the RDN group and 8.57±25 mm Hg in the sham-control group, with a significant difference between the 2 groups of 6.63 mm Hg (95% confidence interval, −11.81 to −1.44; *P*=0.012).[145] Of note, randomization into the RDN and control groups was stratified by race (African American versus Non-African American), that is, the subgroup analysis is solid because randomization was maintained, in contrast to all other subgroup analyses included in the Symplicity HTN-3 article.[145] Differences in the response to BP treatment according to race are well known, and hence many guidelines recommend differential antihypertensive drug strategies in African Americans versus other racial groups.[148,149]

Further debate about the efficacy of RDN is related to the numeric differences between office BP reduction (eg, Symplicity HTN-2 32/12 mm Hg, n=49) and 24-h ABP reduction (eg, Symplicity HTN-2 11/7 mm Hg, n=20).[141] In a pooled analysis, it was shown that in patients with TRH, both office BP and, to a lesser extent, 24-h ABP were significantly reduced, whereas in patients with white coat hypertension, only office BP was significantly reduced.[150] This discrepancy in BP reduction between office BP and 24-h ABP has been observed repeatedly. In the largest reported clinical study, a registry-based analysis, it was found that the disproportionate decreases in office BP versus 24-h ABP were related to the pretreatment BP (which is higher with office BP readings compared with 24-h ABPM) and that the changes in office and 24-h ABPM were not related in a 1:1 fashion.[151]

Most recently, 2 randomized (not sham) controlled trials of RDN in patients with TRH have been published. In the PRAGUE-15 trial, the antihypertensive effects of RDN were compared with those of intensified pharmacological treatment, including spironolactone.[152,153] The reductions in office BP and ABP were comparable in the 2 groups, but 39% of the patients in the pharmacological therapy group experienced adverse effects, for example, hyperkalemia and antiandrogen effects. In the French DENER-HTN study, 106 patients with TRH were randomized to RDN (N=53) or intensified drug treatment (N=53).[154] Baseline-adjusted changes in daytime and nighttime ABP from baseline to 6 month follow-up were significantly greater in the RDN group than in the control group: systolic daytime BP −5.9 mm Hg (*P*=0.0329), systolic nighttime BP −6.3 mm Hg (*P*=0.0296), diastolic daytime BP −3.1 mm Hg (*P*=0.092), and diastolic nighttime BP −3.2 mm Hg (*P*=0.051).[154] Both trials included patients whose hypertension was not truly treatment resistant because office BP and ABP were lowered significantly after uptitrating pharmacological therapy in the intensified drug treatment groups.

Although current knowledge of the effects of RDN is based largely on studies performed with the Symplicity Flex catheter, multi-electrode approaches may reduce the need for catheter manipulation and decrease procedure time. The effects of RDN with various catheters on BP are generally similar, and most of the published trials were uncontrolled (Figure 5).

An unresolved but critical issue in assessing the clinical utility of RDN is to identify a reliable predictor of BP response. Analyses that have focused mainly on clinical characteristics of the patients and technical aspects of the catheters and procedures have failed to identify consistent and reliable predictors, with the exception of baseline systolic BP.[141,150] Baseline BP is positively related to the amount of BP reduction post-RDN according to Wilder's law[155] and regression to the mean effect.

Other clinical effects of RDN, which are at least in part beyond BP reduction, have been reported. These include improvement in glucose metabolism,[156] beneficial effect on end-organ damage, for example, left ventricular hypertrophy,[157] arterial stiffness[158] and albuminuria,[159] attenuation of decline in renal function, and improvement in functional status in patients with congestive HF.

Non-catheter-based approaches of targeting the renal nerves have also been developed. In an adult swine model, a 3-needle delivery device was introduced and 3 different doses of ethanol (each n=3) were injected through the vessel wall into the peri-adventitial tissue in a circumferential manner. There was a dose-dependent decrease in renal parenchymal norepinephrine concentration (0.15 mL/artery, 54%; 0.3 mL/artery, 78%; and 0.6 mL/artery, 88%; all *P*<0.05) after 2 weeks. Histopathologic examination revealed no evidence of device or ethanol-induced intimal injury.[160] An alternative ethanol-based approach was reported in one patient with TRH and end-stage renal disease. Percutaneous ethanol delivery was guided via computer tomography, and ethanol was injected around the renal arteries. After 1 month, office BP was reduced from baseline 172/84 to 143/70 mm Hg. No data about 24-h ABPM, which is considered gold-standard, was provided.[161]

The feasibility of a noninvasive approach to RDN by extracorporeal high-intensity focused ultrasound has been tested in a canine model. Compared with baseline, BP and renal parenchymal noradrenaline concentration were reduced (day 6, −50.1%; day 28, −55.4%; both *P*<0.001), whereas no significant change was observed in the sham-control group. Histopathologic examination demonstrated nerve fiber disruption at day 28 after RDN.[162] The WAVE I trial tested Kona Medical's ultrasound-based Surround Sound® Renal Denervation System (Kona Medical, Menlo Park, CA) in 24 patients with TRH who were taking an average of 4.5 antihypertensive medications and had a mean baseline BP of 190/100 mm Hg. Eighteen focused lesions were applied over 13 minutes to each artery, but for targeting and tracking reasons, a 5F intravascular renal artery catheter

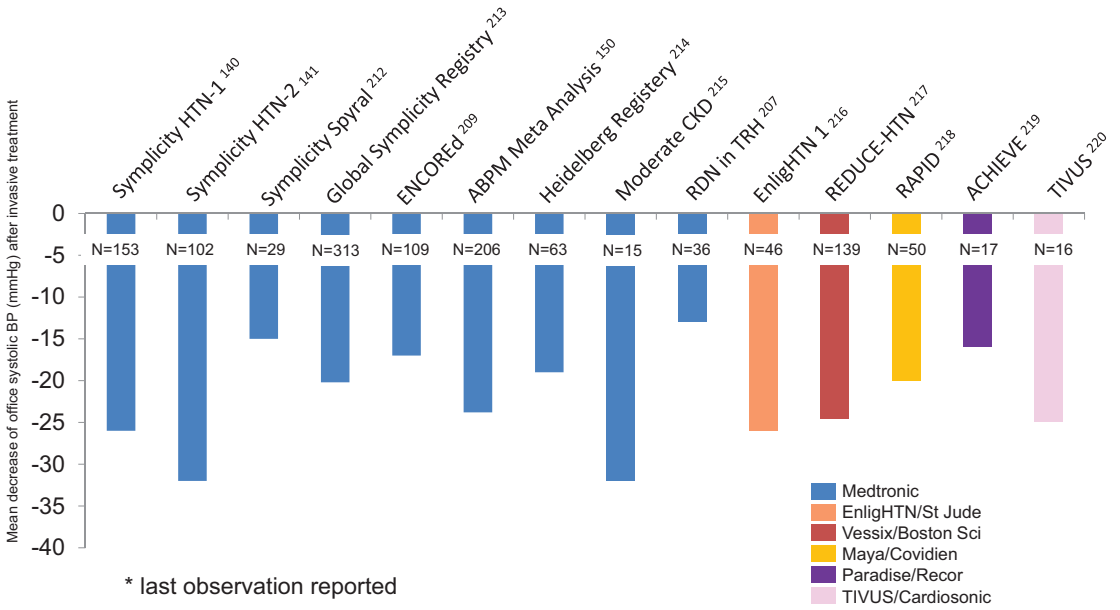


Figure 5. Recent studies of the effects of renal denervation with various catheters on blood pressure. Adapted from Ott and Schmieder[211] with permission of the publisher. Copyright ©2014, Springer. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

had to be used. Office systolic BP was reduced by 29 mm Hg at 6 months after externally focused ultrasound RDN. The WAVE II study, using an optimized treatment protocol (14 externally focused lesions over 3 minutes were applied per side) has been completed, but not yet reported. The WAVE III study used an improved protocol of energy delivery without the need to have a guiding catheter inserted, thus achieving a fully noninvasive RDN approach in humans. First results (n=22), presented at the 2014 Transcatheter Cardiovascular Therapeutics (TCT) meeting, showed an office BP reduction of 29.6/11.8 mm Hg at 3 months after ultrasound RDN.[163] The WAVE IV trial, a prospective, randomized sham-controlled study, in which office and ABP are to be obtained after 6 months, is underway (www.ClinicalTrials.gov: NCT02029885).

Baroreflex Activation Therapy

Knowledge of baroreflex regulation of BP goes back to ancient times. The arteries of the neck were named karotides, based on the Greek rout *karos* (heavy sleep) and *karoun* (to choke, to stupefy) because pressing on these arteries produced sedation. In the 20th century, the role of the carotid baroreflex was demonstrated for short-term BP regulation, but it was assumed to play no role in long-term BP control. However, based on several important studies in animals, interest in the role of the carotid sinus baroreceptor on long-term BP control has returned,[164–166] and a surgical implantable device has been developed to administer BAT via electrical stimulation of the carotid baroreceptors.[167] The prospective nonrandomized DEBut-HT trial was a multicenter European feasibility trial for the early-generation device (Rheos System; CVRx Inc., Minneapolis, MN) performed in 45 patients with TRH (systolic BP ≥160/90 mm Hg, despite ≥3 antihypertensive drugs, including a diuretic). In this proof-of-concept study, there was a reduction of 21±4/12±2 mm Hg (n=37) in office BP at 3 months, with further decreases of 30±6/20±4 (n=26) at 1 year and 33±48/22±26 mm Hg (n=17) at 2 years (all P=<0.005), respectively. There was also a statistically significant reduction in 24-h ABP at 1 year follow-up. In contrast, no BP change was observed in 10 control patients who declined device implantation.[167] In total, 8 serious adverse events (7 procedure-related and 1 device-related) were reported, a number comparable to published complication rates with carotid surgery.[168,169] A substudy of 12 patients from the DEBut-HT trial demonstrated that muscle sympathetic nerve activity and BP were decreased after activation of BAT and increased without activation, providing evidence that reduction of sympathetic outflow is the primary mechanism for BP reduction with BAT.[170]

The double-blind, randomized, parallel-design Rheos Pivotal trial enrolled 256 patients with TRH. One month after Rheos device implantation, patients were randomized in a 2:1 manner to immediate BAT (device on) or delayed BAT (device remained off for 6 months). The prespecified acute primary efficacy end point (proportion of patients achieving BP reduction of ≥10 mm Hg after 6 months with a superiority margin of 20%) was not met, and the secondary efficacy end point (mean change in systolic BP after 6 months) failed statistical significance (group A [device on]: −16±29 versus group B [device off]: −9±29 mm Hg; P=0.08). There was an unexpected difference in systolic BP between preimplant (−1 month) and immediately postimplant (month 0) time points, prompting an additional post hoc analysis of the data. BP reductions from preimplant levels to 6 months postimplant were 26±30 mm Hg in the device on group versus 17±29 mm Hg (P=0.03) in the device off group. The sustained primary efficacy end point, defined as BP reduction of ≥10 mm Hg from months 0 to 12, with ≥50% of BP reduction seen at month 6 (primary end point) was reached. The procedural primary safety end point was not met, mainly because of surgical complications

(4.8%) and transient (4.4%) or residual (4.8%) nerve injuries, but the prespecified criteria of both BAT and device safety were met.[171] After completion of the Rheos Pivotal Trial, participants continued in an open-label, nonrandomized follow-up for an average of 28±9 months. A mean BP reduction of 36/16 mm Hg (P<0.001) was observed in the selected group of long-term responders (n=245, 76%), defined by achieved systolic BP ≤140 mm Hg (≤130 mm Hg for diabetic or renal disease patients) or systolic BP reduction of ≥20 mm Hg from device activation.[172]

A second-generation system of BAT (Barostim neo™) has been designed to address shortcomings of the original device. A single (instead of 5) electrode is implanted at one carotid site, thus reducing the operating field (and hence possible complications). Moreover, the battery is smaller, with an extended life span (≈3 years). In a single-arm open-label study enrolling 30 patients with TRH (based on systolic BP ≥140 mm Hg although on ≥3 antihypertensive drugs, including a diuretic), a BP reduction of 26.0±4.4/12.4±2.5 mm Hg was observed after 6 months and 3 perioperative and 1 long-term procedure-related complications occurred.[173] Upcoming studies (eg, Barostim Hypertension Pivotal Trial, NCT01679132) will clarify the future of this approach to BP reduction.

Animal studies indicate that BAT directly affects autonomic regulation of the heart. Analysis of data from 34 patients pooled from different studies that used BAT demonstrated improvement in left atrial and ventricular structure and function (assessed by echocardiography). Left atrial dimensions and left ventricular mass, wall thickness, and stroke work were reduced, although left ventricular ejection fraction increased.[174] The effects of BAT on metabolic parameters (eg, glucose metabolism) and hypertensive organ damage have not yet been examined.

Carotid Body Ablation

Studies in animal models[175] and human subjects[176] have revealed enhanced carotid body (CB) sensitivity in hypertension, but the mechanisms of this abnormality are not known. CB hypersensitivity has been shown to precede the development of hypertension in SHR[175] and in patients with white-coat hypertension.[176] In a small, randomized, crossover, placebo-controlled study, deactivation of CB chemoreceptors by hyperoxia (respiration with 100% oxygen) attenuated the enhanced muscle sympathetic nerve activity in untreated hypertensive men, but no change was observed in controls.[177] It has also been shown that hyperoxia decreases BP acutely in patients with hypertension, but not in normotensive controls.[178] These data point to a potential pathogenetic role of tonic chemoreceptor drive in the development of sympathetic overactivity in hypertension.[177]

Surgical removal of the CB has been performed in humans for reasons other than hypertension (eg, bronchial asthma and chronic obstructive pulmonary disease [COPD]). A BP fall from 170 to 130 mm Hg was observed 5 days postop and sustained for 6 months after bilateral CB surgery in hypertensive patients, whereas no BP lowering effect was seen in normotensive patients, and a rise in BP was documented in hypotensive patients after bilateral CB resection.[179,180] To date, no study addressing the effect of uni- or bilateral CB resection for hypertension in humans has been completed, but first-in-man studies are ongoing.

Arteriovenous Fistula

A novel mechanistic approach to BP reduction is used by the ROX coupler system (ROX Medical Inc., San Clemente, CA). This self-expanding device creates a 4 mm arteriovenous fistula (AVF) between the iliac artery and vein, generating a sustained calibrated shunt volume (≈ 800 mL/min) within a short period of time (≈1 h). Detailed technical information about deployment of the device is given elsewhere.[181] Several mechanisms are hypothesized to cause BP reduction after creation of an AVF.[182] Reduction in total systemic vascular resistance, despite an increment in cardiac output, is considered to be the key mechanism. Enhanced tissue oxygen delivery caused by increased arterial oxygen content may reduce peripheral and renal chemoreceptor activation and thus decrease sympathetic activity. Reductions in systemic vascular compliance and effective arterial volume may also improve arterial compliance, contributing to a reduced cardiac workload, despite increased cardiac output.[182] Expected adverse effects are induction of venous stenosis and thrombosis and potential worsening/development of right ventricular failure.

The Rox coupler system was originally developed for the treatment of patients with COPD. Early positive results extended the indication to patients with concomitant arterial hypertension. A subset of 24 COPD patients (NCT00832611 and NCT00992680) with an office systolic BP ≥130 mm Hg when on antihypertensive treatment was retrospectively analyzed after the ROX coupler procedure was performed. Compared with baseline (145±12/86±13 mm Hg), systolic and diastolic BP were significantly reduced after 6 (130±18/71±13 mm Hg, P<0.01) and 12 months (132±18/67±13 mm Hg, P<0.01), respectively.[181] No clinical meaningful BP reduction was seen in normotensive COPD patients after creation of an AVF using the ROX coupler.

Based on this first evidence of efficacy of AVF in patients with COPD and coexisting arterial hypertension, the concept was further tested in a small prospective, nonrandomized study enrolling 8 patients with TRH, but without COPD. Compared with baseline, both office BP (175±19/87±14 versus 158±26/74±19 mm Hg) and 24-h ABP (152±17/82±15 versus 142±18/69±14 mm Hg) decreased at 6 months post creation of AVF. Subsequently, the European prospective, open-label, multi-center ROX CONTROL-HTN (NCT01642498) study was initiated to evaluate the ROX Coupler used along with standard drug therapy in 100 patients with TRH without COPD. In the ROX coupler group, office BP decreased by 26.3/20.1 mm Hg (control group 3.7/2.44 mm Hg) and ambulatory BP by 13.5/13.5 mm Hg (control group 0.5/0.1 mm Hg) after 6 months. Reductions were of similar magnitude in those with previous renal denervation.[183] Procedural complications related to arteriovenous coupler placement occurred in N=13 (31%) with venous stenosis occurring in N=12 (29%) of the 42 patients treated.[183] In relation to worsening of hypertension, 5 hospital admissions for hypertensive crisis were reported in 3 (8%) of the 39 control patients, compared with none in the arteriovenous coupler group (P=0.0225).

Neurovascular Decompression

Animal studies have shown that pulsatile compression of the rostral ventrolateral medulla at the root-entry zone of cranial nerves IX and X increases both BP and sympathetic outflow,[184,185] and clinical data suggest that neurosurgical decompression of the rostral ventrolateral medulla (used for neurological disorders) leads to BP reduction.[186] A relationship between relief of hypertension and neurovascular decompression was demonstrated by Geiger et al, who observed improvement in BP control (7 out of 8 patients) 3 months after neurovascular decompression.[187] Sympathetic nerve activity was significantly reduced after microvascular decompression in parallel with the BP decrement. Long-term effects were less promising, however, because hypertension relapsed, and 18 months post intervention, sympathetic nerve activity had increased to preoperative levels.[188,189] Because no long-term clinically significant BP reduction has been demonstrated in a randomized controlled study and special postprocessing software for the analysis of MRI images of the rostral ventrolateral medulla (that are not commonly available) are required to qualify a patient for the procedure, microvascular decompression for treatment of TRH is restricted to compassionate use in patients with severe TRH and proven neurovascular compression using advanced imaging techniques.[190]

Renal Artery Stenting (Revascularization)

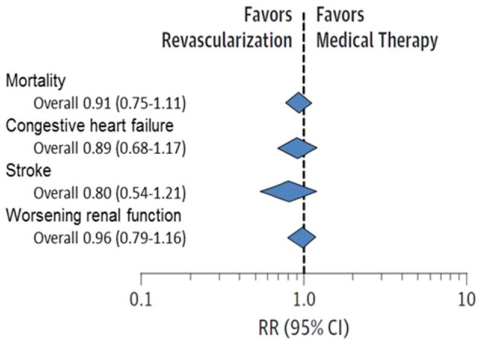
Clinical indications for percutaneous transluminal angioplasty with stenting for renal artery stenosis are controversial. Recent clinical findings from large prospective randomized controlled trials revealed little or no benefit for BP control, preservation of kidney function, or prevention of cardiovascular or renal events, calling into question broad use of renal artery stenting in hypertensive patients with renal artery stenosis.[191–193] In the ASTRAL trial, renal arterial revascularization did not result in a clinically relevant reduction in BP, but did cause a high incidence (17%) of adverse procedure-related complications.[192] However, methodological questions have been raised regarding the inclusion criteria. To enroll a patient in the trial, physicians had to be uncertain whether the patient would profit from the intervention, thus excluding those patients with a clear indication for renal artery stenting and creating a selection bias. For example, 40% of the enrolled patients had <70% narrowing of the renal artery. The STAR trial showed that the primary end point, ≥20% decrement of estimated creatinine clearance, did not differ between medical therapy alone and medical therapy combined with revascularization.[191] However, ≈30% of patients allocated to combined therapy did not undergo revascularization because at the time of angiography, the degree of stenosis was <50%.[191] In the CORAL study of patients with atherosclerotic renal artery stenosis, hypertension, and chronic kidney disease,[193] reduction in systolic BP over time was greater (−2.3 mm Hg; 95% confidence interval, −4.4 to −0.2; P=0.03) in the revascularization group, but this did not result in prevention of cardiovascular or renal events over a median follow-up of 43 months.

All of the studies of renal artery revascularization have been criticized on grounds that they did not critically evaluate the hemodynamic relevance of the renal artery stenosis.[194,195] With the exception of subtotal occlusion of the renal artery, the angiographic degree of renal artery stenosis is a poor reflection of hemodynamic relevance.[196] Hemodynamic relevance (to be suspected if stenosis is >80%) can be assessed by intraarterial pressure measurement or duplex sonography. A diminished resistance index in the cortical tissue reveals hemodynamic relevance, but measurement of blood flow velocity alone is not valid.[197,198] In the CORAL study, translesional renal artery pressure gradients were obtained, but are not yet published.[199] The ongoing controversy about the utility of renal revascularization is portrayed in many publications of pooled data, meta-analyses, and long-term follow-up data. In the absence of more convincing evidence of benefit (Figure 6),[200] it may be wise not to stent as a primary therapeutic option in patients with atherosclerotic renal artery stenosis unless hemodynamic relevance can be demonstrated or rapid deterioration in kidney function or worsening BP is evident.[201–203]

In contrast to atherosclerotic renal artery stenosis, a systematic review and meta-analysis of patients with fibromuscular dysplasia as cause of renal artery stenosis revealed that percutaneous transluminal angioplasty alone (without stenting) improves BP control or even cures hypertension.[204] Further, BP outcome was inversely associated with age. Hence, the European consensus on the diagnosis and management of fibromuscular dysplasia proposes revascularization for hypertension because of fibromuscular dysplasia, especially in patients with recent onset hypertension or TRH.[205]

Future

Published studies of interventional BP lowering treatments were performed almost exclusively in patients with severe TRH, defined as systolic BP ≥160 mm Hg (or ≥150 mm Hg in diabetics), despite treatment with an average of 5 different antihypertensive drugs. However, an expansion to broader populations of TRH (office BP ≥140/90 mm Hg) is being discussed.[206] A small uncontrolled study of patients with true moderate TRH (office BP ≥140/90 mm Hg and 24-h ABP ≥130/80 mm Hg, despite treatment with ≥3 antihypertensive drugs, including a diuretic) showed reductions in office (13/7 mm Hg) and 24-h ABP (14/7 mm Hg) at 6 months after RDN,



Included trials: STAR; ASTRAL; SNARSCG; NITER; CORAL; RASCAD; DRASTIC; EMMA

Figure 6. Renal artery revascularization: updated meta-analysis with the CORAL trial summary estimates of cardiovascular outcomes for revascularization vs medical therapy.

despite a decrease in BP medication. In 51% of these patients, office BP was controlled to <140/90 mm Hg after RDN.[207]

It is generally recognized that several pivotal steps must be taken before adopting RDN as a procedure for BP treatment outside the research setting. First, prospective, randomized, sham-controlled studies have to show the efficacy of RDN in lowering BP in TRH. In this regard, multi-electrode systems may provide more complete, and hence effective, RDN. Second, reliable tools have to be developed to assess the completeness of RDN. Third, because the BP response to RDN varies greatly from patient to patient,[141,208,209] a reliable clinical predictor of BP response to RDN is needed to improve patient selection. Fourth, the efficacy of RDN in improving clinical outcomes has to be demonstrated. It is likely that global registry data will be needed to reach this final critical goal.[210]

Acknowledgments

Samantha Giordano, PhD, Postdoctoral Fellow, Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham designed Figures 1–4 and assisted Suzanne Oparil with the literature searches.

Disclosures

S. Oparil reports individual and institutional payment related to board membership from Bayer, Daiichi Sankyo, Novartis, Medtronic, and Takeda; individual consulting fees from Backbeat, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, Daiichi Sankyo, Eli Lilly, Medtronic, Merck, Pfizer, and Takeda; receipt of institutional grant funding from AstraZeneca, Daiichi Sankyo, Eisai Inc, Gilead, Medtronic, Merck, Novartis, Takeda Global Research, and Development Inc; individual payment for lectures from Daiichi Sankyo, Merck, Novartis, and Pfizer; individual and institutional payment for development of educational presentations from American Society of Hypertension (ASH)/ASH Accredited Hypertension Sales Representative (AHSR) Program (Daiichi Sankyo); and individual and institutional payment from Amarin Pharma Inc, Daiichi Sankyo, and LipoScience Inc for educational grant(s) for the Annual UAB Vascular Biology and Hypertension Symposium. Dr Oparil reports these relationships for the past 60 months. R.E. Schmieder is an employee of the Free State of Bavaria, University Hospital, Friedrich Alexander-University Erlangen-Nürnberg, has received Speaker fees, Consultancy and Advisory Board fees, from AstraZeneca, Berlin Chemie AG, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Kona Medical, Medtronic, Novartis, Rox Medical, Servier, Recor, Takeda Pharmaceuticals, Terumo. The University Hospital has received Research funding from AstraZeneca, Boehringer Ingelheim, BMBF (Bundesministerium für Bildung und Forschung), Bristol Myers Squibb, Daiichi Sankyo, Medtronic Novartis, and Roxmedical.

References

1. Food and Drug Administration and the Department of Health and Human Services. Notice. Guidance for Industry on Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims; Availability. 15 March 2011;76 FR 14024:1–12. (accessible at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm075072.pdf).
2. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension*. 2011;57:1076–1080. doi: 10.1161/HYPERTENSIONAHA.111.170308.
3. Sim JJ, Bhandari SK, Shi J, Liu IL, Calhoun DA, McGlynn EA, Kalantar-Zadeh K, Jacobsen SJ. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clin Proc*. 2013;88:1099–1107. doi: 10.1016/j.mayocp.2013.06.017.
4. Calhoun DA, Booth JN III, Oparil S, Irvin MR, Shimbo D, Lackland DT, Howard G, Safford MM, Muntner P. Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. *Hypertension*. 2014;63:451–458. doi: 10.1161/HYPERTENSIONAHA.113.02026.
5. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, Samani NJ, Gupta P, Madira W, Stanley A, Williams B. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart*. 2014;100:855–861. doi: 10.1136/heartjnl-2013-305063.
6. Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to recommended therapy. *Hypertens Res*. 2011;34:87–90. doi: 10.1038/hr.2010.183.
7. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens*. 2013;31:766–774. doi: 10.1097/HJH.0b013e32835e2286.
8. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, Das SR, Halm EA, Kaplan NM, Vongpatanasin W. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. *J Am Coll Cardiol*. 2014;63:834–835. doi: 10.1016/j.jacc.2013.10.067.
9. Strauch B, Petrák O, Zelinka T, Rosa J, Somlóová Z, Indra T, Chytil L, Marešová V, Kurcová I, Holaj R, Wichterle D, Widimský J Jr. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens*. 2013;31:2455–2461. doi: 10.1097/HJH.0b013e3283652c61.
10. Ruilope LM. Aldosterone, hypertension, and cardiovascular disease: an endless story. *Hypertension*. 2008;52:207–208. doi: 10.1161/HYPERTENSIONAHA.108.111211.
11. Kawamoto T, Mitsuuchi Y, Toda K, Yokoyama Y, Miyahara K, Miura S. Ohnishi T, Ichikawa Y, Nakao K, Imura H, Ulick S, Shizuta, Y. Role of steroid 11β-hydroxylase and steroid 18-hydroxylase in the biosynthesis of glucocorticoids and mineralocorticoids in humans. *Proc Natl Acad Sci USA*. 1992;89:1458–1462.
12. Schumacher CD, Steele RE, Brunner HR. Aldosterone synthase inhibition for the treatment of hypertension and the derived mechanistic requirements for a new therapeutic strategy. *J Hypertens*. 2013;31:2085–2093. doi: 10.1097/HJH.0b013e328363570c.
13. Hargovan M, Ferro A. Aldosterone synthase inhibitors in hypertension: current status and future possibilities. *JRSM Cardiovasc Dis*. 2014;3:2048004014522440. doi: 10.1177/2048004014522440.
14. Yin L, Hu Q, Emmerich J, Lo MM, Metzger E, Ali A, Hartmann RW. Novel pyridyl- or isoquinolinyl-substituted indolines and indoles as potent and selective aldosterone synthase inhibitors. *J Med Chem*. 2014;57:5179–5189. doi: 10.1021/jm500140c.
15. Cranston WI, Juel-Jensen BE. The effects of spironolactone and chlorthalidone on arterial pressure. *Lancet*. 1962;1:1161–1164.
16. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens*. 2003;16:925–930.
17. Vaclavik J, Sedlak R, Plachy M, Navratil K, Plasek J, Husar R, Kocianova E, Taborsky M. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT)–study protocol. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2011;155:143–148.
18. Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension*. 2007;49:839–845. doi: 10.1161/01.HYP.0000259805.18468.8c.
19. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117:e510–e526. doi: 10.1161/CIRCULATIONAHA.108.189141.
20. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717. doi: 10.1056/NEJM199909023411001.
21. Corvol P, Michaud A, Menard J, Freifeld M, Mahoudeau J. Antiandrogenic effect of spirolactones: mechanism of action. *Endocrinology*. 1975;97:52–58. doi: 10.1210/endo-97-1-52.
22. Colussi G, Catena C, Sechi LA. Spironolactone, eplerenone and the new aldosterone blockers in endocrine and primary hypertension. *J Hypertens*. 2013;31:3–15. doi: 10.1097/HJH.0b013e3283599b6a.

23. Garthwaite SM, McMahon EG. The evolution of aldosterone antagonists. *Mol Cell Endocrinol*. 2004;217:27–31. doi: 10.1016/j.mce.2003.10.005.
24. Kolkhof P, Borden SA. Molecular pharmacology of the mineralocorticoid receptor: prospects for novel therapeutics. *Mol Cell Endocrinol*. 2012;350:310–317. doi: 10.1016/j.mce.2011.06.025.
25. Dietz JD, Du S, Bolten CW, Payne MA, Xia C, Blinn JR, Funder JW, Hu X. A number of marketed dihydropyridine calcium channel blockers have mineralocorticoid receptor antagonist activity. *Hypertension*. 2008;51:742–748. doi: 10.1161/HYPERTENSIONAHA.107.103580.
26. Fagart J, Hillisch A, Huyet J, Bärfacker L, Fay M, Pleiss U, Pook E, Schäfer S, Rafestin-Oblin ME, Kolkhof P. A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule. *J Biol Chem*. 2010;285:29932–29940. doi: 10.1074/jbc.M110.131342.
27. Bärfacker L, Kuhl A, Hillisch A, Grosser R, Figueroa-Pérez S, Heckroth H, Nitsche A, Ergüden JK, Gielen-Haertwig H, Schlemmer KH, Mittendorf J, Paulsen H, Platzek J, Kolkhof P. Discovery of BAY 94-8862: a nonsteroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases. *ChemMedChem*. 2012;7:1385–1403. doi: 10.1002/cmdc.201200081.
28. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Bärfacker L, Eitner F, Albrecht-Küpper B, Schäfer S. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol*. 2014;64:69–78. doi: 10.1097/FJC.0000000000000091.
29. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, Nowack C, Kolkhof P, Kim SY, Zannad F. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J*. 2013;34:2453–2463. doi: 10.1093/eurheartj/eht187.
30. Pitt B, Filippatos G, Gheorghiade M, Kober L, Krum H, Ponikowski P, Nowack C, Kolkhof P, Kim SY, Zannad F. Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. *Eur J Heart Fail*. 2012;14:668–675. doi: 10.1093/eurjhf/hfs061.
31. Chai W, Danser AH. Why are mineralocorticoid receptor antagonists cardioprotective? *Naunyn Schmiedebergs Arch Pharmacol*. 2006;374:153–162. doi: 10.1007/s00210-006-0107-9.
32. Schiffrin EL. Effects of aldosterone on the vasculature. *Hypertension*. 2006;47:312–318. doi: 10.1161/01.HYP.0000201443.63240.a7.
33. Amar L, Azizi M, Menard J, Peyrard S, Plouin PF. Sequential comparison of aldosterone synthase inhibition and mineralocorticoid blockade in patients with primary aldosteronism. *J Hypertens*. 2013;31:624–629.
34. Jansen PM, van den Meiracker AH, Jan Danser AH. Aldosterone synthase inhibitors: pharmacological and clinical aspects. *Curr Opin Investig Drugs*. 2009;10:319–326.
35. Azizi M, Amar L, Menard J. Aldosterone synthase inhibition in humans. *Nephrol Dial Transplant*. 2013;28:36–43. doi: 10.1093/ndt/gfs388.
36. Ménard J, Pascoe L. Can the dextroenantiomer of the aromatase inhibitor fadrozole be useful for clinical investigation of aldosterone-synthase inhibition? *J Hypertens*. 2006;24:993–997. doi: 10.1097/01.hjh.0000226183.98439.b3.
37. Ménard J, Gonzalez MF, Guyene TT, Bissery A. Investigation of aldosterone-synthase inhibition in rats. *J Hypertens*. 2006;24:1147–1155. doi: 10.1097/01.hjh.0000226205.65442.f2.
38. Lea WB, Kwak ES, Luther JM, Fowler SM, Wang Z, Ma J, Fogo AB, Brown NJ. Aldosterone antagonism or synthase inhibition reduces end-organ damage induced by treatment with angiotensin and high salt. *Kidney Int*. 2009;75:936–944. doi: 10.1038/ki.2009.9.
39. Ménard J, Watson C, Rebello S, Zhang YM, Dole WP. Hormonal and electrolyte responses to the aldosterone synthase inhibitor LCI699 in sodium depleted healthy subjects. The American College of Cardiology Foundation *J Am Coll Cardiol*. 2010;55(10s1):A61.E583.
40. Amar L, Azizi M, Menard J, Peyrard S, Watson C, Plouin PF. Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. *Hypertension*. 2010;56:831–838. doi: 10.1161/HYPERTENSIONAHA.110.157271.
41. Calhoun DA, White WB, Krum H, Guo W, Bermann G, Trapani A, Lefkowitz MP, Ménard J. Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active-controlled phase 2 trial. *Circulation*. 2011;124:1945–1955. doi: 10.1161/CIRCULATIONAHA.111.029892.
42. Andersen K, Hartman D, Peppard T, Hermann D, Van Ess P, Lefkowitz M, Trapani A. The effects of aldosterone synthase inhibition on aldosterone and cortisol in patients with hypertension: a phase II, randomized, double-blind, placebo-controlled, multicenter study. *J Clin Hypertens (Greenwich)*. 2012;14:580–587. doi: 10.1111/j.1751-7176.2012.00667.x.
43. Karns AD, Bral JM, Hartman D, Peppard T, Schumacher C. Study of aldosterone synthase inhibition as an add-on therapy in resistant hypertension. *J Clin Hypertens (Greenwich)*. 2013;15:186–192. doi: 10.1111/jch.12051.
44. Hu Q, Yin L, Hartmann RW. Aldosterone synthase inhibitors as promising treatments for mineralocorticoid dependent cardiovascular and renal diseases. *J Med Chem*. 2014;57:5011–5022. doi: 10.1021/jm401430e.
45. Oparil S, Haber E. The renin-angiotensin system (second of two parts). *N Engl J Med*. 1974;291:446–457. doi: 10.1056/NEJM197408292910905.
46. Ferreira AJ, Murça TM, Fraga-Silva RA, Castro CH, Raizada MK, Santos RA. New cardiovascular and pulmonary therapeutic strategies based on the Angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis. *Int J Hypertens*. 2012;2012:147825. doi: 10.1155/2012/147825.
47. Foulquier S, Steckelings UM, Unger T. Impact of the AT(2) receptor agonist C21 on blood pressure and beyond. *Curr Hypertens Rep*. 2012;14:403–409. doi: 10.1007/s11906-012-0291-6.
48. Jiang F, Yang J, Zhang Y, Dong M, Wang S, Zhang Q, Liu FF, Zhang K, Zhang C. Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets. *Nat Rev Cardiol*. 2014;11:413–426. doi: 10.1038/nrcardio.2014.59.
49. Fraga-Silva RA, Ferreira AJ, Dos Santos RA. Opportunities for targeting the angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor pathway in hypertension. *Curr Hypertens Rep*. 2013;15:31–38. doi: 10.1007/s11906-012-0324-1.
50. Jankowski V, Vanholder R, van der Giet M, et al. Mass-spectrometric identification of a novel angiotensin peptide in human plasma. *Arterioscler Thromb Vasc Biol*. 2007;27:297–302. doi: 10.1161/01.ATV.0000253889.09765.5f.
51. Ocaranza MP, Moya J, Barrientos V, et al. Angiotensin-(1-9) reverses experimental hypertension and cardiovascular damage by inhibition of the angiotensin converting enzyme/Ang II axis. *J Hypertens*. 2014;32:771–783. doi: 10.1097/HJH.0000000000000094.
52. Ferreira AJ, Shenoy V, Qi Y, Fraga-Silva RA, Santos RA, Katovich MJ, Raizada MK. Angiotensin-converting enzyme 2 activation protects against hypertension-induced cardiac fibrosis involving extracellular signal-regulated kinases. *Exp Physiol*. 2011;96:287–294. doi: 10.1113/expphysiol.2010.055277.
53. Kulemina LV, Ostrov DA. Prediction of off-target effects on angiotensin-converting enzyme 2. *J Biomol Screen*. 2011;16:878–885. doi: 10.1177/1087057111413919.
54. Ferreira AJ, Shenoy V, Yamazato Y, Sriramula S, Francis J, Yuan L, Castellano RK, Ostrov DA, Oh SP, Katovich MJ, Raizada MK. Evidence for angiotensin-converting enzyme 2 as a therapeutic target for the prevention of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179:1048–1054. doi: 10.1164/rccm.200811-1678OC.
55. Ferreira AJ, Santos RA, Raizada MK. Angiotensin-(1-7)/angiotensin-converting enzyme 2/mas receptor axis and related mechanisms. *Int J Hypertens*. 2012;2012:690785. doi: 10.1155/2012/690785.
56. Treml B, Neu N, Kleinsasser A, Gritsch C, Finsterwalder T, Geiger R, Schuster M, Janzek E, Loibner H, Penninger J, Loeckinger A. Recombinant angiotensin-converting enzyme 2 improves pulmonary blood flow and oxygenation in lipopolysaccharide-induced lung injury in piglets. *Crit Care Med*. 2010;38:596–601. doi: 10.1097/CCM.0b013e3181c03009.
57. Oudit GY, Liu GC, Zhong J, Basu R, Chow FL, Zhou J, Loibner H, Janzek E, Schuster M, Penninger JM, Herzenberg AM, Kassiri Z, Scholey JW. Human recombinant ACE2 reduces the progression of diabetic nephropathy. *Diabetes*. 2010;59:529–538.
58. Haschke M, Schuster M, Poglitsch M, Loibner H, Salzberg M, Bruggisser M, Penninger J, Krähenbühl S. Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects. *Clin Pharmacokinet*. 2013;52:783–792. doi: 10.1007/s40262-013-0072-7.
59. Petty WJ, Miller AA, McCoy TP, Gallagher PE, Tallant EA, Torti FM. Phase I and pharmacokinetic study of angiotensin-(1-7), an endogenous antiangiogenic hormone. *Clin Cancer Res*. 2009;15:7398–7404. doi: 10.1158/1078-0432.CCR-09-1957.
60. Rodgers KE, Oliver J, diZerega GS. Phase I/II dose escalation study of angiotensin 1-7 [A(1-7)] administered before and after chemotherapy in patients with newly diagnosed breast cancer. *Cancer Chemother Pharmacol*. 2006;57:559–568. doi: 10.1007/s00280-005-0078-4.
61. Kluskens LD, Nelemans SA, Rink R, de Vries L, Meter-Arkema A, Wang Y, Walther T, Kuipers A, Moll GN, Haas M. Angiotensin-(1-7) with thioether bridge: an angiotensin-converting enzyme-resistant, potent angiotensin-(1-7) analog. *J Pharmacol Exp Ther*. 2009;328:849–854. doi: 10.1124/jpet.108.146431.

62. Marques FD, Melo MB, Souza LE, Irigoyen MC, Sinisterra RD, de Sousa FB, Savergnini SQ, Braga VB, Ferreira AJ, Santos RA. Beneficial effects of long-term administration of an oral formulation of Angiotensin-(1-7) in infarcted rats. *Int J Hypertens*. 2012;2012:795452. doi: 10.1155/2012/795452.
63. Santos SH, Andrade JM. Angiotensin 1-7: a peptide for preventing and treating metabolic syndrome. *Peptides*. 2014;59:34–41. doi: 10.1016/j.peptides.2014.07.002.
64. Singh Y, Singh K, Sharma PL. Effect of combination of renin inhibitor and Mas-receptor agonist in DOCA-salt-induced hypertension in rats. *Mol Cell Biochem*. 2013;373:189–194. doi: 10.1007/s11010-012-1489-2.
65. Savergnini SQ, Ianzer D, Carvalho MB, Ferreira AJ, Silva GA, Marques FD, Peluso AA, Beiman M, Cojocaru G, Cohen Y, Almeida AP, Rotman G, Santos RA. The novel Mas agonist, CGEN-856S, attenuates isoproterenol-induced cardiac remodeling and myocardial infarction injury in rats. *PLoS One*. 2013;8:e57757. doi: 10.1371/journal.pone.0057757.
66. Lautner RQ, Villela DC, Fraga-Silva RA, et al. Discovery and characterization of alamandine: a novel component of the renin-angiotensin system. *Circ Res*. 2013;112:1104–1111. doi: 10.1161/CIRCRESAHA.113.301077.
67. Ganten D, Hermann K, Bayer C, Unger T, Lang RE. Angiotensin synthesis in the brain and increased turnover in hypertensive rats. *Science*. 1983;221:869–871.
68. Gao J, Marc Y, Iturrioz X, Leroux V, Balavoine F, Llorens-Cortes C. A new strategy for treating hypertension by blocking the activity of the brain renin-angiotensin system with aminopeptidase A inhibitors. *Clin Sci (Lond)*. 2014;127:135–148. doi: 10.1042/CS20130396.
69. Réaux A, de Mota N, Zini S, Cadel S, Fournié-Zaluski MC, Roques BP, Corvol P, Llorens-Cortès C. PC18, a specific aminopeptidase N inhibitor, induces vasopressin release by increasing the half-life of brain angiotensin III. *Neuroendocrinology*. 1999;69:370–376. doi: 54439.
70. Marc Y, Gao J, Balavoine F, Michaud A, Roques BP, Llorens-Cortes C. Central antihypertensive effects of orally active aminopeptidase A inhibitors in spontaneously hypertensive rats. *Hypertension*. 2012;60:411–418. doi: 10.1161/HYPERTENSIONAHA.112.190942.
71. Bodineau L, Frugière A, Marc Y, Claperon C, Llorens-Cortes C. Aminopeptidase A inhibitors as centrally acting antihypertensive agents. *Heart Fail Rev*. 2008;13:311–319. doi: 10.1007/s10741-007-9077-3.
72. Balavoine F, Azizi M, Bergerot D, De Mota N, Patouret R, Roques BP, Llorens-Cortes C. Randomised, double-blind, placebo-controlled, dose-escalating phase I study of QGC001, a centrally acting aminopeptidase a inhibitor prodrug. *Clin Pharmacokinet*. 2014;53:385–395. doi: 10.1007/s40262-013-0125-y.
73. Corti R, Burnett JC Jr, Rouleau JL, Ruschitzka F, Lüscher TF. Vasopeptidase inhibitors: a new therapeutic concept in cardiovascular disease? *Circulation*. 2001;104:1856–1862.
74. Bevan EG, Connell JM, Doyle J, Carmichael HA, Davies DL, Lorimer AR, McInnes GT. Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension. *J Hypertens*. 1992;10:607–613.
75. von Lueder TG, Sangaralingham SJ, Wang BH, Kompa AR, Atar D, Burnett JC Jr, Krum H. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. *Circ Heart Fail*. 2013;6:594–605. doi: 10.1161/CIRCHEARTFAILURE.112.000289.
76. Richards AM, Wittert GA, Crozier IG, Spiner EA, Yandle TG, Ikram H, et al. Chronic inhibition of endopeptidase 24.11 in essential hypertension: evidence for enhanced atrial natriuretic peptide and angiotensin II. *J Hypertens*. 1993;4:407–416.
77. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol*. 2010;50:401–414. doi: 10.1177/0091270009343932.
78. Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255–1266. doi: 10.1016/S0140-6736(09)61966-8.
79. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103–111.
80. Kario K, Sun N, Chiang FT, Supasyndh O, Baek SH, Inubushi-Molessa A, Zhang Y, Gotou H, Lefkowitz M, Zhang J. Efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Asian patients with hypertension: a randomized, double-blind, placebo-controlled study. *Hypertension*. 2014;63:698–705. doi: 10.1161/HYPERTENSIONAHA.113.02002.
81. Eguchi K, Kario K, Hoshide Y, Hoshide S, Ishikawa J, Morinari M, Ishikawa S, Shimada K. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. *Am J Hypertens*. 2004;17:112–117.
82. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387–1395. doi: 10.1016/S0140-6736(12)61227-6.
83. Jhund PS, Claggett B, Packer M, Zile MR, Voors AA, Pieske B, Lefkowitz M, Shi V, Bransford T, McMurray JJ, Solomon SD. Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. *Eur J Heart Fail*. 2014;16:671–677. doi: 10.1002/ejhf.76.
84. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013;15:1062–1073. doi: 10.1093/eurjhf/hft052.
85. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:1062–1064.
86. Jessup M. Neprilysin inhibition–a novel therapy for heart failure. *N Engl J Med*. 2014;371:1062–1064. doi: 10.1056/NEJMe1409898.
87. Williams B, Cockcroft JR, Kario K, Zappe DH, Cardenas P, Hester A, Brunel P, Zhang J. Rationale and study design of the prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker measuring arterial stiffness in the elderly (PARAMETER) study. *BMJ Open*. 2014;4:e004254. doi: 10.1136/bmjopen-2013-004254.
88. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, Kropf J, Eber B. Validation of a brachial cuff-based method for estimating central systolic blood pressure. *Hypertension*. 2011;58:825–832. doi: 10.1161/HYPERTENSIONAHA.111.176313.
89. Dickstein K, De Voogd HJ, Miric MP, Willenbrock R, Mitrovic V, Pacher R, Koopman PA. Effect of single doses of SLV306, an inhibitor of both neutral endopeptidase and endothelin-converting enzyme, on pulmonary pressures in congestive heart failure. *Am J Cardiol*. 2004;94:237–239. doi: 10.1016/j.amjcard.2004.03.074.
90. Thöne-Reinke C, Simon K, Richter CM, Godes M, Neumayer HH, Thormählen D, Hocher B. Inhibition of both neutral endopeptidase and endothelin-converting enzyme by SLV306 reduces proteinuria and urinary albumin excretion in diabetic rats. *J Cardiovasc Pharmacol*. 2004;44 Suppl 1:S76–S79.
91. Van der Meer I, Benigni A, Parvanova A, Iliev I, Sharma S, Cruz J, et al. Pressure control by combined ECE/NEP inhibitor on top of losartan: a randomized, cross-over, placebo-controlled clinical trial in patients with type 2 diabetes and albuminuria. Twelfth International Conference on Endothelin; 2011. p. 50.
92. Seed A, Kuc RE, Maguire JJ, Hillier C, Johnston F, Essers H, de Voogd HJ, McMurray J, Davenport AP. The dual endothelin converting enzyme/neutral endopeptidase inhibitor SLV-306 (daglutril), inhibits systemic conversion of big endothelin-1 in humans. *Life Sci*. 2012;91:743–748. doi: 10.1016/j.lfs.2012.03.022.
93. Parvanova A, van der Meer IM, Iliev I, Perna A, Gaspari F, Trevisan R, Bossi A, Remuzzi G, Benigni A, Ruggenenti P; Daglutril in Diabetic Nephropathy Study Group. Effect on blood pressure of combined inhibition of endothelin-converting enzyme and neutral endopeptidase with daglutril in patients with type 2 diabetes who have albuminuria: a randomised, crossover, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2013;1:19–27. doi: 10.1016/S2213-8587(13)70029-9.
94. Tikkanen I, Tikkanen T, Cao Z, Allen TJ, Davis BJ, Lassila M, Casley D, Johnston CI, Burrell LM, Cooper ME. Combined inhibition of neutral endopeptidase with angiotensin converting enzyme or endothelin converting enzyme in experimental diabetes. *J Hypertens*. 2002;20:707–714.
95. Tabrizchi R. SLV-306. Solvay. *Curr Opin Investig Drugs*. 2003;4:329–332.

96. Edelson JD, Makhlina M, Silvester KR, Vengurlekar SS, Chen X, Zhang J, Koziol-White CJ, Cooper PR, Hallam TJ, Hay DW, Panettieri RA Jr. In vitro and in vivo pharmacological profile of PL-3994, a novel cyclic peptide (Hept-cyclo(Cys-His-Phe-d-Ala-Gly-Arg-d-Nle-Asp-Arg-Ile-Ser-Cys)-Tyr-[Arg mimetic]-NH(2)) natriuretic peptide receptor-A agonist that is resistant to neutral endopeptidase and acts as a bronchodilator. *Pulm Pharmacol Ther*. 2013;26:229–238. doi: 10.1016/j.pupt.2012.11.001.
97. Li Y, Sarkar O, Brochu M, Anand-Srivastava MB. Natriuretic peptide receptor-C attenuates hypertension in spontaneously hypertensive rats: role of nitroxidative stress and Gi proteins. *Hypertension*. 2014;63:846–855. doi: 10.1161/HYPERTENSIONAHA.113.01772.
98. Morisseau C, Hammock BD. Epoxide hydrolases: mechanisms, inhibitor designs, and biological roles. *Annu Rev Pharmacol Toxicol*. 2005;45:311–333. doi: 10.1146/annurev.pharmtox.45.120403.095920.
99. Neckář J, Kopkan L, Husková Z, Kolář F, Papoušek F, Kramer HJ, Hwang SH, Hammock BD, Imig JD, Malý J, Netuka I, Ošťádal B, Červenka L. Inhibition of soluble epoxide hydrolase by cis-4-[4-(3-adamantan-1-ylureido)cyclohexyl-oxy]benzoic acid exhibits antihypertensive and cardioprotective actions in transgenic rats with angiotensin II-dependent hypertension. *Clin Sci (Lond)*. 2012;122:513–525. doi: 10.1042/CS20110622.
100. Xu D, Li N, He Y, Timofeyev V, Lu L, Tsai HJ, Kim IH, Tuteja D, Mateo RK, Singapuri A, Davis BB, Low R, Hammock BD, Chiamvimonvat N. Prevention and reversal of cardiac hypertrophy by soluble epoxide hydrolase inhibitors. *Proc Natl Acad Sci U S A*. 2006;103:18733–18738. doi: 10.1073/pnas.0609158103.
101. Anandan SK, Webb HK, Chen D, et al. 1-(1-acetyl-piperidin-4-yl)-3-adamantan-1-yl-urea (AR9281) as a potent, selective, and orally available soluble epoxide hydrolase inhibitor with efficacy in rodent models of hypertension and dysglycemia. *Bioorg Med Chem Lett*. 2011;21:983–988. doi: 10.1016/j.bmcl.2010.12.042.
102. Wong K, Zhang L-N, Vincelette J, Chen D, Tran V, Mehra U, Gless R, Anandan S-K, Webb HK, MacIntyre U, Wang Y-X. A novel inhibitor of soluble epoxide hydrolase, AR9281, improves glucose homeostasis in diet-induced obese mice. American Diabetes Society 69th Scientific Sessions. New Orleans. *Diabetes*. 2009;58:A436 (1698-A).
103. Chen D, Whitcomb R, MacIntyre E, Tran V, Do ZN, Sabry J, Patel DV, Anandan SK, Gless R, Webb HK. Pharmacokinetics and pharmacodynamics of AR9281, an inhibitor of soluble epoxide hydrolase, in single- and multiple-dose studies in healthy human subjects. *J Clin Pharmacol*. 2012;52:319–328. doi: 10.1177/0091270010397049.
104. A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Exploratory, 28-Day Study to Examine the Effects of AR9281 on Blood Pressure and Glucose Tolerance in Patients With Mild to Moderate Hypertension and Impaired Glucose Tolerance (accessible at http://clinicaltrials.gov/ct2/show/record/NCT00847899).
105. Imig JD, Hammock BD. Soluble epoxide hydrolase as a therapeutic target for cardiovascular diseases. *Nat Rev Drug Discov*. 2009;8:794–805. doi: 10.1038/nrd2875.
106. Couvineau A, Laburthe M. VPAC receptors: structure, molecular pharmacology and interaction with accessory proteins. *Br J Pharmacol*. 2012;166:42–50. doi: 10.1111/j.1476-5381.2011.01676.x.
107. Henning RJ, Sawmiller DR. Vasoactive intestinal peptide: cardiovascular effects. *Cardiovasc Res*. 2001;49:27–37.
108. Linz D, Wirth K, Linz W, Heuer HO, Frick W, Hofmeister A, Heinelt U, Arndt P, Schwahn U, Böhm M, Ruetten H. Antihypertensive and laxative effects by pharmacological inhibition of sodium-proton-exchanger subtype 3-mediated sodium absorption in the gut. *Hypertension*. 2012;60:1560–1567. doi: 10.1161/HYPERTENSIONAHA.112.201590.
109. Spencer AG, Labonte ED, Rosenbaum DP, et al. Intestinal inhibition of the Na+/H+ exchanger 3 prevents cardiorenal damage in rats and inhibits Na+ uptake in humans. *Sci Transl Med*. 2014;6:227ra36. doi: 10.1126/scitranslmed.3007790.
110. Beliaev A, Learmonth DA, Soares-da-Silva P. Synthesis and biological evaluation of novel, peripherally selective chromanyl imidazolethione-based inhibitors of dopamine beta-hydroxylase. *J Med Chem*. 2006;49:1191–1197. doi: 10.1021/jm051051f.
111. Almeida L, Nunes T, Costa R, Rocha JF, Vaz-da-Silva M, Soares-da-Silva P. Etamicastat, a novel dopamine β-hydroxylase inhibitor: tolerability, pharmacokinetics, and pharmacodynamics in patients with hypertension. *Clin Ther*. 2013;35:1983–1996. doi: 10.1016/j.clinthera.2013.10.012.
112. Igreja B, Pires NM, Bonifácio MJ, Loureiro AI, Fernandes-Lopes C, Wright LC, Soares-da-Silva P. Blood pressure-decreasing effect of etamicastat alone and in combination with antihypertensive drugs in the spontaneously hypertensive rat. *Hypertens Res*. 2015;38:30–38. doi: 10.1038/hr.2014.143.
113. Helmer OM. Studies on renin antibodies. *Circulation*. 1958;17:648–652.
114. Michel JB, Guettier C, Reade R, Sayah S, Corvol P, Ménard J. Immunologic approaches to blockade of the renin-angiotensin system: a review. *Am Heart J*. 1989;117:756–767.
115. Hong F, Quan WY, Pandey R, Yi S, Chi L, Xia LZ, Yuan M, Ming L. A vaccine for hypertension based on peptide AngI-R: a pilot study. *Int J Cardiol*. 2011;148:76–84. doi: 10.1016/j.ijcard.2009.10.027.
116. Downham MR, Auton TR, Rosul A, Sharp HL, Sjöström L, Rushton A, Richards JP, Mant TG, Gardiner SM, Bennett T, Glover JF. Evaluation of two carrier protein-angiotensin I conjugate vaccines to assess their future potential to control high blood pressure (hypertension) in man. *Br J Clin Pharmacol*. 2003;56:505–512.
117. Brown MJ, Coltart J, Gunewardena K, Ritter JM, Auton TR, Glover JF. Randomized double-blind placebo-controlled study of an angiotensin immunotherapeutic vaccine (PMD3117) in hypertensive subjects. *Clin Sci (Lond)*. 2004;107:167–173. doi: 10.1042/CS20030381.
118. Ambühl PM, Tissot AC, Fulurija A, et al. A vaccine for hypertension based on virus-like particles: preclinical efficacy and phase I safety and immunogenicity. *J Hypertens*. 2007;25:63–72. doi: 10.1097/HJH.0b013e32800ff5d6.
119. Tissot AC, Maurer P, Nussberger J, Sabat R, Pfister T, Ignatenko S, Volk HD, Stocker H, Müller P, Jennings GT, Wagner F, Bachmann MF. Effect of immunisation against angiotensin II with CYT006-AngQb on ambulatory blood pressure: a double-blind, randomised, placebo-controlled phase IIa study. *Lancet*. 2008;371:821–827. doi: 10.1016/S0140-6736(08)60381-5.
120. Brown MJ. Success and failure of vaccines against renin-angiotensin system components. *Nat Rev Cardiol*. 2009;6:639–647. doi: 10.1038/nrcardio.2009.156.
121. Biotechnology reports biochemical findings from phase IIa study with hypertension vaccine Cyt006–AngQb *Medical News Today* [online], http://www.medicalnewstoday.com/articles/ 155303.php (2009).
122. Bairwa M, Pilania M, Gupta V, Yadav K. Hypertension Vaccine may be a boon to millions in developing world. *Hum Vaccin Immunother*. 2014;10:708–713.
123. Chen X, Qiu Z, Yang S, Ding D, Chen F, Zhou Y, Wang M, Lin J, Yu X, Zhou Z, Liao Y. Effectiveness and safety of a therapeutic vaccine against angiotensin II receptor type 1 in hypertensive animals. *Hypertension*. 2013;61:408–416. doi: 10.1161/HYPERTENSIONAHA.112.201020.
124. Li LD, Tian M, Liao YH, Zhou ZH, Wei F, Zhu F, Wang M, Wang B, Wei YM. Effect of active immunization against angiotensin II type 1 (AT1) receptor on hypertension & arterial remodelling in spontaneously hypertensive rats (SHR). *Indian J Med Res*. 2014;139:619–624.
125. Nakagami F, Koriyama H, Nakagami H, Osako MK, Shimamura M, Kyutoku M, Miyake T, Katsuya T, Rakugi H, Morishita R. Decrease in blood pressure and regression of cardiovascular complications by angiotensin II vaccine in mice. *PLoS One*. 2013;8:e60493. doi: 10.1371/journal.pone.0060493.
126. Ou X, Guo L, Wu J, Mi K, Yin N, Zhang G, Li H, Sun M. Construction, expression and immunogenicity of a novel anti-hypertension angiotensin II vaccine based on hepatitis A virus-like particle. *Hum Vaccin Immunother*. 2013;9:1191–1199. doi: 10.4161/hv.23940.
127. Graves SW, Williams GH. An endogenous ouabain-like factor associated with hypertensive pregnant women. *J Clin Endocrinol Metab*. 1984;59:1070–1074. doi: 10.1210/jcem-59-6-1070.
128. Gusdon JP Jr, Buckalew VM Jr, Hennessy JF. A digoxin-like immunoreactive substance in preeclampsia. *Am J Obstet Gynecol*. 1984;150:83–85.
129. Lam GK, Hopoate-Sitake M, Adair CD, Buckalew VM, Johnson DD, Lewis DF, Robinson CJ, Saade GR, Graves SW. Digoxin antibody fragment, antigen binding (Fab), treatment of preeclampsia in women with endogenous digitalis-like factor: a secondary analysis of the DEEP Trial. *Am J Obstet Gynecol*. 2013;209:119.e1–119.e6. doi: 10.1016/j.ajog.2013.04.010.
130. Ishkaraeva-Yakovleva VV, Fedorova OV, Solodovnikova NG, Frolova EV, Bzhelyansky AM, Emelyanov IV, Adair CD, Zazerskaya IE, Bagrov AY. DigiFab interacts with endogenous cardiotonic steroids and reverses preeclampsia-induced Na/K-ATPase inhibition. *Reprod Sci*. 2012;19:1260–1267. doi: 10.1177/1933719112447124.
131. Krep H, Price DA, Soszynski P, Tao QF, Graves SW, Hollenberg NK. Volume sensitive hypertension and the digoxin-like factor. Reversal by a Fab directed against digoxin in DOCA-salt hypertensive rats. *Am J Hypertens*. 1995;8:921–927. doi: 10.1016/0895-7061(95)00181-N.

132. Goodlin RC. Antidigoxin antibodies in eclampsia. *N Engl J Med*. 1988;318:518–519. doi: 10.1056/NEJM198802253180815.
133. Adair CD, Buckalew VM, Graves SW, et al. Digoxin immune fab treatment for severe preeclampsia. *Am J Perinatol*. 2010;27:655–662. doi: 10.1055/s-0030-1249762.
134. Paidas MJ, Sibai BM, Triche EW, Frieling J, Lowry S; PRESERVE-1 Study Group. Exploring the role of antithrombin replacement for the treatment of preeclampsia: a prospective randomized evaluation of the safety and efficacy of recombinant antithrombin in very preterm preeclampsia (PRESERVE-1). *Am J Reprod Immunol*. 2013;69:539–544. doi: 10.1111/aji.12091.
135. Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357. doi: 10.1097/01.hjh.0000431740.32696.cc.
136. Esler M, Jennings G, Korner P, Willett I, Dudley F, Hasking G, Anderson W, Lambert G. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension*. 1988;11:3–20.
137. DiBona GF, Kopp UC. Neural control of renal function. *Physiol Rev*. 1997;77:75–197.
138. Katholi RE. Renal nerves in the pathogenesis of hypertension in experimental animals and humans. *Am J Physiol*. 1983;245:F1–14.
139. Stella A, Zanchetti A. Functional role of renal afferents. *Physiol Rev*. 1991;71:659–682.
140. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275–1281. doi: 10.1016/S0140-6736(09)60566-3.
141. Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet*. 2010;376:1903–1909.
142. Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*. 2014;383:622–629. doi: 10.1016/S0140-6736(13)62192-3.
143. Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, Mahfoud F, Schlaich MP. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. *Eur Heart J*. 2014;35:1752–1759. doi: 10.1093/eurheartj/ehu209.
144. Persu A, Renkin J, Thijs L, Staessen JA. Renal denervation: ultima ratio or standard in treatment-resistant hypertension. *Hypertension*. 2012;60:596–606. doi: 10.1161/HYPERTENSIONAHA.112.195263.
145. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393–1401. doi: 10.1056/NEJMoa1402670.
146. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J*. 2015;36:219–227. doi: 10.1093/eurheartj/ehu441.
147. Bhatt DL, Bakris GL. Renal denervation for resistant hypertension. *N Engl J Med*. 2014;371:184. doi: 10.1056/NEJMc1405677.
148. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520. doi: 10.1001/jama.2013.284427.
149. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2014;16:14–26. doi: 10.1111/jch.12237.
150. Mahfoud F, Ukena C, Schmieder RE, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation*. 2013;128:132–140. doi: 10.1161/CIRCULATIONAHA.112.000949.
151. Schmieder RE, Schmidt ST, Riemer T, Dechend R, Hagedorn I, Senges J, Messerli FH, Zeymer U. Disproportional decrease in office blood pressure compared with 24-hour ambulatory blood pressure with antihypertensive treatment: dependency on pretreatment blood pressure levels. *Hypertension*. 2014;64:1067–1072. doi: 10.1161/HYPERTENSIONAHA.113.03140.
152. Mahfoud F, Ruilope LM, Böhm M, Schmieder RE. Aldosterone antagonists and renal denervation: friends or foes? *Hypertension*. 2015;65:280–282. doi: 10.1161/HYPERTENSIONAHA.114.04119.
153. Rosa J, Widimský P, Toušek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the prague-15 study. *Hypertension*. 2015;65:407–413. doi: 10.1161/HYPERTENSIONAHA.114.04019.
154. Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardized antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicenter, open-label, randomized controlled trial. *Lancet*. 2015;pii: S0140-6736(14)61942–5. doi: 10.1016/S0140-6736(14)61942–5. [Epub ahead of print].
155. Messerli FH, Bangalore S, Schmieder RE. Wilder's principle: pre-treatment value determines post-treatment response. *Eur Heart J*. 2014;pii: ehu467. [Epub ahead of print].
156. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation*. 2011;123:1940–1946. doi: 10.1161/CIRCULATIONAHA.110.991869.
157. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol*. 2012;59:901–909. doi: 10.1016/j.jacc.2011.11.034.
158. Brandt MC, Reda S, Mahfoud F, Lenski M, Böhm M, Hoppe UC. Effects of renal sympathetic denervation on arterial stiffness and central hemodynamics in patients with resistant hypertension. *J Am Coll Cardiol*. 2012;60:1956–1965. doi: 10.1016/j.jacc.2012.08.959.
159. Ott C, Mahfoud F, Schmid A, Ditting T, Veelken R, Ewen S, Ukena C, Uder M, Böhm M, Schmieder RE. Improvement of albuminuria after renal denervation. *Int J Cardiol*. 2014;173:311–315. doi: 10.1016/j.ijcard.2014.03.017.
160. Fischell TA, Vega F, Raju N, Johnson ET, Kent DJ, Ragland RR, Fischell DR, Almany SL, Ghazarossian VE. Ethanol-mediated perivascular renal sympathetic denervation: preclinical validation of safety and efficacy in a porcine model. *EuroIntervention*. 2013;9:140–147. doi: 10.4244/EIJV9I1A20.
161. Streitparth F, Gebauer B, Nickel P, Reinke P, Freyhardt P, Wieners G, Hamm B, Günther RW. Percutaneous computer tomography-guided ethanol sympathicolysis for the treatment of resistant arterial hypertension. *Cardiovasc Intervent Radiol*. 2014;37:513–518. doi: 10.1007/s00270-014-0850-0.
162. Wang Q, Guo R, Rong S, et al. Noninvasive renal sympathetic denervation by extracorporeal high-intensity focused ultrasound in a pre-clinical canine model. *J Am Coll Cardiol*. 2013;61:2185–2192. doi: 10.1016/j.jacc.2013.02.050.
163. Ormiston JA, Anderson T, Brinton TJ, et al. TCT-412 non-invasive renal denervation using externally delivered focused ultrasound: early experience using Doppler based imaging tracking and targeting for treatment. *J Am Coll Cardiol*. 2014;64(11_S):. doi:10.1016/j.jacc.2014.07.461.
164. Lohmeier TE, Irwin ED, Rossing MA, Serdar DJ, Kieval RS. Prolonged activation of the baroreflex produces sustained hypotension. *Hypertension*. 2004;43:306–311. doi: 10.1161/01.HYP.0000111837.73693.9b.
165. Thrasher TN. Effects of chronic baroreceptor unloading on blood pressure in the dog. *Am J Physiol Regul Integr Comp Physiol*. 2005;288:R863–R871. doi: 10.1152/ajpregu.00489.2004.
166. Lohmeier TE, Dwyer TM, Irwin ED, Rossing MA, Kieval RS. Prolonged activation of the baroreflex abolishes obesity-induced hypertension. *Hypertension*. 2007;49:1307–1314. doi: 10.1161/HYPERTENSIONAHA.107.087874.
167. Scheffers IJ, Kroon AA, Schmidli J, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. *J Am Coll Cardiol*. 2010;56:1254–1258. doi: 10.1016/j.jacc.2010.03.089.
168. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*. 1995;273:1421–1428.
169. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, Taylor DW, Haynes RB, Finan JW, Hachinski VC, Barnett HJ. The North American symptomatic carotid endarterectomy trial: surgical results in 1415 patients. *Stroke*. 1999;30:1751–1758.

170. Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S, Peters T, Sweep FC, Haller H, Pichlmaier AM, Luft FC, Jordan J. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension*. 2010;55:619–626. doi: 10.1161/HYPERTENSIONAHA.109.140665.
171. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, de Leeuw PW, Sica DA. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol*. 2011;58:765–773. doi: 10.1016/j.jacc.2011.06.008.
172. Bakris GL, Nadim MK, Haller H, Lovett EG, Schafer JE, Bisognano JD. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. *J Am Soc Hypertens*. 2012;6:152–158. doi: 10.1016/j.jash.2012.01.003.
173. Hoppe UC, Brandt MC, Wachter R, Beige J, Rump LC, Kroon AA, Cates AW, Lovett EG, Haller H. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. *J Am Soc Hypertens*. 2012;6:270–276. doi: 10.1016/j.jash.2012.04.004.
174. Bisognano JD, Kaufman CL, Bach DS, Lovett EG, de Leeuw P; DEBuT-HT and Rheos Feasibility Trial Investigators. Improved cardiac structure and function with chronic treatment using an implantable device in resistant hypertension: results from European and United States trials of the Rheos system. *J Am Coll Cardiol*. 2011;57:1787–1788. doi: 10.1016/j.jacc.2010.11.048.
175. Tan ZY, Lu Y, Whiteis CA, Simms AE, Paton JF, Chapleau MW, Abboud FM. Chemoreceptor hypersensitivity, sympathetic excitation, and overexpression of ASIC and TASK channels before the onset of hypertension in SHR. *Circ Res*. 2010;106:536–545. doi: 10.1161/CIRCRESAHA.109.206946.
176. Trzebski A, Tafil M, Zoltowski M, Przybylski J. Increased sensitivity of the arterial chemoreceptor drive in young men with mild hypertension. *Cardiovasc Res*. 1982;16:163–172.
177. Siński M, Lewandowski J, Przybylski J, Bidiuk J, Abramczyk P, Ciarka A, Gaciong Z. Tonic activity of carotid body chemoreceptors contributes to the increased sympathetic drive in essential hypertension. *Hypertens Res*. 2012;35:487–491. doi: 10.1038/hr.2011.209.
178. Sinski M, Lewandowski J, Przybylski J, Zalewski P, Symonides B, Abramczyk P, Gaciong Z. Deactivation of carotid body chemoreceptors by hyperoxia decreases blood pressure in hypertensive patients. *Hypertens Res*. 2014;37:858–862. doi: 10.1038/hr.2014.91.
179. Nakayama K. Surgical removal of the carotid body for bronchial asthma. *Dis Chest*. 1961;40:595–604.
180. Winter B, Whipp BJ. Immediate effects of bilateral carotid body resection on total respiratory resistance and compliance in humans. *Adv Exp Med Biol*. 2004;551:15–21.
181. Faul J, Schoors D, Brouwers S, Scott B, Jerrentrup A, Galvin J, Luitjens S, Dolan E. Creation of an iliac arteriovenous shunt lowers blood pressure in chronic obstructive pulmonary disease patients with hypertension. *J Vasc Surg*. 2014;59:1078–1083. doi: 10.1016/j.jvs.2013.10.069.
182. Burchell AE, Lobo MD, Sulke N, Sobotka PA, Paton JF. Arteriovenous anastomosis: is this the way to control hypertension? *Hypertension*. 2014;64:6–12. doi: 10.1161/HYPERTENSIONAHA.114.02925.
183. Lobo MD, Sobotka PA, Stanton A, et al; for the ROX CONTROL HTN Investigators. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet*. 2015 Jan 22. pii: S0140-6736(14)62053–5. doi: 10.1016/S0140-6736(14)62053–5. [Epub ahead of print].
184. Jannetta PJ, Segal R, Wolfson SK Jr, Dujovny M, Semba A, Cook EE. Neurogenic hypertension: etiology and surgical treatment. II. Observations in an experimental nonhuman primate model. *Ann Surg*. 1985;202:253–261.
185. Morimoto S, Sasaki S, Miki S, Kawa T, Itoh H, Nakata T, Takeda K, Nakagawa M, Naruse S, Maeda T. Pulsatile compression of the rostral ventrolateral medulla in hypertension. *Hypertension*. 1997;29:514–518.
186. Yamamoto I, Yamada S, Sato O. Microvascular decompression for hypertension–clinical and experimental study. *Neurol Med Chir (Tokyo)*. 1991;31:1–6.
187. Geiger H, Naraghi R, Schobel HP, Frank H, Sterzel RB, Fahlbusch R. Decrease of blood pressure by ventrolateral medullary decompression in essential hypertension. *Lancet*. 1998;352:446–449.
188. Frank H, Schobel HP, Heusser K, Geiger H, Fahlbusch R, Naraghi R. Long-term results after microvascular decompression in essential hypertension. *Stroke*. 2001;32:2950–2955.
189. Frank H, Heusser K, Geiger H, Fahlbusch R, Naraghi R, Schobel HP. Temporary reduction of blood pressure and sympathetic nerve activity in hypertensive patients after microvascular decompression. *Stroke*. 2009;40:47–51. doi: 10.1161/STROKEAHA.108.518670.
190. Naraghi R, Geiger H, Crnac J, Huk W, Fahlbusch R, Engels G, Luft FC. Posterior fossa neurovascular anomalies in essential hypertension. *Lancet*. 1994;344:1466–1470.
191. Bax L, Woittiez AJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med*. 2009;150:840–8, W150.
192. Wheatley K, Ives N, Gray R, et al; on behalf of ASTRAL Investigators. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361:1953–1962.
193. Cooper CJ, Murphy TP, Cutlip DE, et al; CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med*. 2014;370:13–22. doi: 10.1056/NEJMoa1310753.
194. Leesar M, White C, De Bruyne B. Stenting for renal-artery stenosis. *N Engl J Med*. 2014;370:1853. doi: 10.1056/NEJMc1402687#SA3.
195. Mahé G, Jaquinandi V. Stenting for renal-artery stenosis. *N Engl J Med*. 2014;370:1853–1854. doi: 10.1056/NEJMc1402687#SA4.
196. De Bruyne B, Manoharan G, Pijls NH, Verhamme K, Madaric J, Bartunek J, Vanderheyden M, Heyndrickx GR. Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol*. 2006;48:1851–1855. doi: 10.1016/j.jacc.2006.05.074.
197. Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, Galanski M, Koch KM, Haller H. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med*. 2001;344:410–417. doi: 10.1056/NEJM200102083440603.
198. Radermacher J, Ellis S, Haller H. Renal resistance index and progression of renal disease. *Hypertension*. 2002;39:699–703.
199. Murphy TP, Dworkin LD, Cooper CJ. Stenting for renal-artery stenosis. *N Engl J Med*. 2014;370:1854–1855. doi: 10.1056/NEJMc1402687.
200. Bavry AA, Kapadia SR, Bhatt DL, Kumbhani DJ. Renal artery revascularization: updated meta-analysis with the CORAL trial. *JAMA Intern Med*. 2014;174:1849–1851. doi: 10.1001/jamainternmed.2014.4332.
201. Weinberg I, Keyes MJ, Giri J, Rogers KR, Olin JW, White CJ, Jaff MR. Blood pressure response to renal artery stenting in 901 patients from five prospective multicenter FDA-approved trials. *Catheter Cardiovasc Interv*. 2014;83:603–609. doi: 10.1002/ccd.25263.
202. Schmieder RE. To stent or not to stent. *Nephrologe*. 2014;9:228–229.
203. Chrysant GS, Bates MC, Sullivan TM, Bachinsky WB, Popma JJ, Peng L, Omran HL, Jaff MR; HERCULES Investigators. Proper patient selection yields significant and sustained reduction in systolic blood pressure following renal artery stenting in patients with uncontrolled hypertension: long-term results from the HERCULES trial. *J Clin Hypertens (Greenwich)*. 2014;16:497–503. doi: 10.1111/jch.12341.
204. Trinquart L, Mounier-Vehier C, Sapoval M, Gagnon N, Plouin PF. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. *Hypertension*. 2010;56:525–532. doi: 10.1161/HYPERTENSIONAHA.110.152918.
205. Persu A, Giavarini A, Touzé E, Januszewicz A, Sapoval M, Azizi M, Barral X, Jeunemaitre X, Morganti A, Plouin PF, de Leeuw P; ESH Working Group Hypertension and the Kidney. European consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens*. 2014;32:1367–1378. doi: 10.1097/HJH.0000000000000213.
206. Vemulapalli S, Ard J, Bakris GL, et al. Proceedings from Duke resistant hypertension think tank. *Am Heart J*. 2014;167:775–88.e1. doi: 10.1016/j.ahj.2014.02.008.
207. Ott C, Mahfoud F, Schmid A, Ditting T, Sobotka PA, Veelken R, Spies A, Ukena C, Laufs U, Uder M, Böhm M, Schmieder RE. Renal denervation in moderate treatment-resistant hypertension. *J Am Coll Cardiol*. 2013;62:1880–1886. doi: 10.1016/j.jacc.2013.06.023.
208. Brinkmann J, Heusser K, Schmidt BM, Menne J, Klein G, Bauersachs J, Haller H, Sweep FC, Diedrich A, Jordan J, Tank J. Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertensive patients: prospective case series. *Hypertension*. 2012;60:1485–1490. doi: 10.1161/HYPERTENSIONAHA.112.201186.
209. Persu A, Jin Y, Azizi M, et al; European Network COordinating research on Renal Denervation (ENCOReD). Blood pressure changes

after renal denervation at 10 European expert centers. *J Hum Hypertens*. 2014;28:150–156. doi: 10.1038/jhh.2013.88.
210. Pathak A, Ewen S, Fajadet J, Honton B, Mahfoud F, Marco J, Schlaich M, Schmieder R, Tsioufis K, Ukena C, Zeller T. From SYMPLICITY HTN-3 to the renal denervation global registry: where do we stand and where should we go? *EuroIntervention*. 2014;10:21–23. doi: 10.4244/EIJV10I1A4.
211. Ott C, Schmieder RE. Invasive treatment of resistant hypertension: present and future. *Curr Hypertens Rep*. 2014;16:488. doi: 10.1007/s11906-014-0488-y.
212. Walton T, Hardin S, Rothman M, Whitbourn R. Renal artery denervation with a new simultaneous multielectrode catheter for treatment of resistant hypertension: Six month results from the symplicity spyral first-in-man study. *EuroPCR*. 2014;Euro14A–OP209.
213. Mahfoud F. Reduction in office blood pressure after renal denervation in a large real world patient population with uncontrolled hypertension: Interim results from the global Symplicity registry. Paper Presented at: the 2014 ACC Scientific Sessions. Washington DC. 2014.
214. Vogel B, Kirchberger M, Zeier M, Stoll F, Meder B, Saure D, Andrassy M, Mueller OJ, Hardt S, Schwenger V, Strothmeyer A, Katus HA, Blessing E. Renal sympathetic denervation therapy in the real world: results from the Heidelberg registry. *Clin Res Cardiol*. 2014;103:117–124. doi: 10.1007/s00392-013-0627-5.
215. Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, Sobotka PA, Böhm M, Cremers B, Esler MD, Schlaich MP. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol*. 2012;23:1250–1257. doi: 10.1681/ASN.2011111062.
216. Papademetriou V, Tsioufis CP, Sinhal A, Chew DP, Meredith IT, Malaiapan Y, Worthley MI, Worthley SG. Catheter-based renal denervation for resistant hypertension: 12-month results of the EnligHTN I first-in-human study using a multielectrode ablation system. *Hypertension*. 2014;64:565–572. doi: 10.1161/HYPERTENSIONAHA.114.03605.
217. Sievert H, On behalf of the REDUCE-HTN Investigators. Reduce-htn clinical study: Interim 6- and 12-month data. TCT. 2013:Oral presentation.
218. Verheye S, Ormiston J, Kuck KH, Bergmann M, Sievert H, Torsello G, Dens JAY, Grube E, Colombo A, Vogel B, Voskuil M, Daemen J. Safety and effectiveness of catheter-based renal sympathetic denervation for the treatment of resistant hypertension: 12-month results of the rapid study. *EuroPCR*. 2014:14A–OP208.
219. Zeller T, Andersson B, Bohm M, Kuck KH, Sievert H, Graf T, Kahlert P, Daemen J. The paradise renal denervation system: Initial clinical results from the achieve study. *EuroPCR*. 2014:14A–OP205.
220. Shetty S, Blessing E, Roenschein U, Scheinert D, Diehm N, Jonas M. Renal denervation using the novel therapeutic intra-vascular ultrasound (tivus) catheter system - preliminary report of first-in-man safety and performance study. *EuroPCR*. 2014:14A–OP206.

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

New Approaches in the Treatment of Hypertension

Suzanne Oparil and Roland E. Schmieder

Circ Res. 2015;116:1074-1095
doi: 10.1161/CIRCRESAHA.116.303603
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571